Parvovirus B19 infection in five European countries: seroepidemiology, force of infection and maternal risk of infection

Non Peer-reviewed author version

Mossong, J.; HENS, Niel; Friederichs, V.; Davidkin, I.; Broman, M.; Litwinska, A.; Siennicka, J.; Trzcinska, A.; Van Damme, P.; Beutels, P.; Vyse, A.; SHKEDY, Ziv; AERTS, Marc; Massari, M. & Gabutti, G. (2008) Parvovirus B19 infection in five European countries: seroepidemiology, force of infection and maternal risk of infection. In: EPIDEMIOLOGY AND INFECTION, 136(8). p. 1059-1068.

DOI: 10.1017/S0950268807009661
Handle: http://hdl.handle.net/1942/8566

Parvovirus B19 infection in 5 European countries: seroepidemiology, force of infection and maternal risk of infection

J. Mossong[1], N. Hens[2], V. Friederichs[3], I. Davidkin[4], M. Broman[4], B. Litwinska[5], J. Siennicka[5], A. Trzcinska[5], P. van Damme[6], P. Beutels[6], A. Vyse[7], Z. Shkedy[2], M. Aerts[2], M. Massari[8], G. Gabutti[9]

[1] Laboratoire Nationale de Santé, Luxembourg

[2] Universiteit of Hasselt, Belgium

[3] Centre de recherché public - Santé, Luxembourg

[4] National Public Health Institute, KTL, Finland

[5] National Institute of Hygiene, Poland

[6] University of Antwerp, Belgium

[7] Health Protection Agency, United Kingdom

[8] Istituto Superiore de Sanità, Italy

[9] University of Ferrara, Italy

Author responsible correspondence and to whom requests for reprints should be addressed: Joël Mossong, Microbiology, Laboratoire National de Santé, PO Box 1102, L-1011 Luxembourg, Luxembourg, email : joel.mossong@lns.etat.lu

Running head: Seroepidemiology of parvovirus B19 in Europe

Summary

We conducted a seroprevalence survey in Belgium, Finland, England & Wales, Italy and Poland on 13449 serum samples broadly representative in terms of geography and age. Samples were tested for the presence of immunoglobulin G antibody using a enzyme immuno-assay. The age-specific risk of infection was estimated using parametric and non-parametric statistical modeling. The age-specific risk in all 5 countries was highest in children aged 7-9 years and lower in adults. The average proportion of women in child-bearing age susceptible to parvovirus B19 infection and the risk of a pregnant women acquiring B19 infection during pregnancy was estimated to be 26% and 0.61%,in Belgium, 38% and 0.69% in England & Wales, 43.5% and 1.24% in Finland, 39.9% and 0.92% in Italy and 36.8% and 1.58% in Poland, respectively. Our study indicates substantial epidemiological differences in Europe regarding parvovirus B19 infection.

Introduction

Parvovirus B19 is the infectious agent of erythema infectiosum, commonly known as slapped cheek syndrome or fifth disease [1]. The disease in children and teenagers is usually mild, but infection with parvovirus B19 during pregnancy has been associated with miscarriage, intrauterine fetal death, fetal anemia and non-immune hydrops [2]. Parvovirus B19 infection has also been associated with acute arthropathy in adults [3], with aplastic crisis in sickle-cell disease patients and with chronic anemia in immunodeficient patients [4]. It is mainly transmitted through the respiratory route, but blood-borne and nosocomial transmission events have been documented [4, 5].

While some basic features of the epidemiology of parvovirus B19 infection in temperate countries are known – infection in childhood is common, infection continues at a lower rate in adulthood, epidemics occur at intervals of a few years [4] - very few studies have actually tried to address and estimate the burden of parvovirus B19 infection for the population as a whole in a more precise and systematic manner. Most studies have predictably focused on risk factors in pregnant women because of the risk to the fetus [6].

Although vaccine development has shown promising initial results [7],, there is currently no vaccine available against parvovirus B19. Because immunoglobulin G (IgG) antibodies following infection are thought to persist for a lifetime [4], seroprevalence profiles from large cross-sectional surveys provide estimates of past exposure to parvovirus B19 infection and can be used to derive the age specific yearly risk of acquiring infection – also known as the force of infection - which has been found to vary with age for a number of infectious diseases [8].

The principal aim of our study was to determine age-specific B19 seroprevalence profiles in 5 European countries by testing blood samples from large serum banks for the presence of IgG antibodies against parvovirus B19 using the same assay to avoid possible inter-assay variation. This study allowed us to compare the epidemiology of parvovirus B19 in the 5 countries by estimating age-specific seroprevalence of parvovirus B19 infection, derive the

age-specific force of infection and determine the overall risk of women having a parvovirus B19 infection during pregnancy by linking our analysis with publicly available demographic data.

Methods

Study population

In five countries (Belgium, England and Wales, Finland, Italy, Poland) testing for parvovirus B19 IgG antibody was performed on large representative national serum banks during 2005-2006. The sera were collected between 1995 and 2004 and were obtained from residual sera collected during routine laboratory. Sera covered all age groups, were approximately evenly distributed between males and females and were geographically representative of each country (see Table 1).

Comparison of two commercial parvovirus B19 IgG assays

Prior to testing the large serum banks we compared the diagnostic performance of two commercial parvovirus B19 IgG enzyme immune-assays - Mikrogen recomwell (Martinsried, Germany) and Biotrin (Dublin, Ireland) on a subsample of 180 Finnish sera having the same age distribution as the final Finnish data used in this study. Sera were tested according to the manufacturers' instructions and discordant results were retested using the Mikrogen western blot assay (recomblot Parvovirus B19 IgG).

Main serum bank testing

The main serum banks were tested using the recomwell Parvovirus B19 IgG assay kits (Mikrogen) from the same batch by five laboratories in each country according to the manufacturer's instructions. Quantitative results were calculated from the optical densities and plate dependent corrections according to manufacturer's instructions:.samples with antibody activity levels >24 U/ml were considered positive, samples with antibody activity levels<20 were considered negative and samples in between were considered equivocal.

The cut off defined by the manufacturer to discriminate negative from positive samples was checked and validated using histograms of the quantitative results on a logarithmic scale.

Modeling seroprevalence and force of infection

Seroprevalence was estimated separately for each country, sex and age group. 95% confidence intervals were calculated based on the exact binomial method.

Parametric and nonparametric curves with confidence bands for the seroprevalence and force of infection were estimated using the equation

$$P(a) = 1 - \exp(-\int_0^a \lambda(a')da') \qquad \text{(Eq. 1)}$$

where $P(a)$ is the prevalence and $\lambda(a)$ is the force of infection at age. For the parametric estimates of the force of infection we initially chose a piecewise constant model with intervals [0.5,5), [5,10), [10,25), [25,40) and [40+) assuming that maternal antibodies last until the age of 6 months. The age categories correspond approximately to the 20-, 40-, 60- and 80- percentiles of the age distribution of serum donors.

For the nonparametric estimates of the seroprevalence and force of infection, local quadratic polynomials were used with a data driven automatic procedure to choose the local bandwidth [9]. 95% confidence intervals were obtained by a bootstrap procedure with 1000 replications.

Estimating number of parvovirus B19 infections in pregnant women

The age dependent number of infections in pregnancy was estimated using Eurostat data of live births in 1997 (http://epp.eurostat.cec.eu.int), the most recent year with data available for all 5 countries. The number of pregnant women of age a with B19 infection, $I(a)$, was estimated using the equation [10]

$$I(a) = 0.75\ \lambda(a)\ (1\text{-}P(a))\ L(a) \qquad \text{(Eq. 2)}$$

where $\lambda(a)$ is the estimated force of infection at age a and $1\text{-}P(a)$ is the estimated proportion of susceptibles of age a according to the local quadratic model, $L(a)$ is the number of live births for mothers of age a, and the scalar 0.75 represents the duration of 9 months of an average pregnancy in yearly units.

Results

Comparison of assays

Qualitative agreement (the proportion of concordant results: 91%) and quantitative correlation (0.87) between the two assays was high. The major reason for discordant results was sera positive by the Biotrin EIA and negative by the Mikrogen EIA. Donors of discordant sera were significantly younger than donors of sera with concordant results. Antibody reactivity in the Biotrin assay on these sera was also significantly lower than for concordant positive results. Retesting with the Mikrogen western blot assay tended to agree with the Mikrogen EIA assay. Seroprofiles by age of tested sera were similar between the two assays except in the youngest age groups, where the Biotrin assay estimated a slightly higher seroprevalence. Based on these results, the Mikrogen assay was chosen for testing the five main serum banks.

Analysis of the cut-off used for the main serum bank

For each country's main serum bank, the Mikrogen assay produced two distinct populations of seropositives and seronegatives (Figure 1). The equivocal range indicated by the manufacturer was found in the trough between the two populations modes, such that there was no need to apply further modeling techniques as suggested in a previous study based on a different laboratory assay [10]. For further analysis all samples in the equivocal range were excluded (see table 1). The distributions of quantitative antibody data was very similar between countries, although the data from Finland displayed a smaller variation within each distribution of positives and negatives and the fraction of the data of positives from England & Wales appear to yield higher titres than found in any of the other countries.

Seroprevalence and the force of infection

Figure 2 a)-e) shows the seroprevalence profiles in the 5 countries which follow a broadly similar pattern. In all countries we observed that in the first three age classes (i.e. those aged 1 to 3), the seroprevalence data and model estimates appear to be constant or

decrease even to some extent resulting in locally negative estimates of the force of infection. Again in all 5 countries, the seroprevalence then increases quite rapidly in older children and teenagers. In older teenagers and young adults the seroprevalences start to level off and reach a plateau for young adults followed by a further increase in the age classes above about 25-30 years of age. There is little difference between the seroprevalence estimates of parametric and non-parametric models.

The force of infection estimates in figure 2 f)-j) show a similar picture, with a peak occurring among children, followed by a decline in teenagers and a marginal increase again in the late twenties and thirties. Again the parametric and non-parametric models have similar shapes although it is obvious that the nonparametric curves of the local quadratic method allow more smooth and flexible shapes than the parametric piece-wise constant method.

When the seroprevalence curves are compared between the countries in more detail, some interesting and unexpected features emerge (Figure 3 a). It is striking that for persons between 5 and 45 years of age, B19 seroprevalence for Finland is always lowest, whereas the prevalence in Belgium is highest and Poland, Italy and England and Wales intermediate. In Finland and Belgium, the difference in seroprevalence estimates in these age groups are statistically significant (data not shown), suggesting that the epidemiology could be different in these two countries. Based on estimates from the local quadratic model, the seroprevalences range from 35% in Finland to 58% in Belgium at age 10, from 51% in Finland to 75% in Belgium at age 20 and from 57% in Finland to 73% in Belgium at age 30, which is approximately the mean age of pregnant women (see figure 4). The plateau in the seroprevalence for young adults seems to be more pronounced for Belgium, England and Wales and Italy than for Finland and Poland.

The force of infection estimates of the local quadratic model reflect the differences observed in the seroprevalence profiles for children and adolescents. In Belgium there was quite a

narrow and sharp peak at 7 years with a maximum value of 0.14. England and Wales and Finland had very similar looking peaks at 9 years with a maximum value of 0.09 per year while for Italy this peak occurs at 8 years with a maximum value of 0.10 per year. The peak in Poland was much wider than in other countries with a force of infection estimate of approximately 0.06 for children aged 8 to 14 years. Interestingly the Belgian data was unique in showing a shoulder effect in the age group 12-18 with a force of infection estimate of approximately 0.08. The lowest force of infection estimates among adults was found at age 24 years (Belgium, England & Wales, Italy), 22 years (Finland) and 27 years (Poland). Following this decline in early adulthood, the quadratic model suggested another slight increase of the force of infection for the age groups 25 to 40 years. The polish data was unique in sustaining a much higher force of infection (0.03) in persons aged 40 years and older, compared to the other countries.

Sex-specific differences within countries in seroprevalence and force of infection estimates were generally minor and mostly non-significant except in the age group of 40+ year olds, where the force of infection estimates tended to be slightly higher for women than for men.

Estimating the burden of parvovirus B19 infections in pregnant women

Whereas the age distribution of pregnant women leading to live births in Belgium, Finland and Italy is very symmetric with a mode at 28-30 years, the distribution in England and Wales differs mainly because of a higher proportion of teenage pregnancies and the age distribution of pregnancies in Poland is skewed to the left (Figure 4). In Finland and Italy, the expected distribution of B19 cases occurring in pregnant mothers follows very closely the actual age distribution of pregnant mothers. In Poland, due to the higher force of infection in older teenagers, the peak of expected B19 infections occurs two years earlier than the peak of actual pregnancies. Most interestingly in Belgium and England & Wales two distinct peaks appear, the first in teenagers due to a higher force of infection and a high rate of teenage

pregnancies in the UK and a second peak which follows more closely the distribution of pregnant women.

Table 2 shows some summary measures of the total burden of parvovirus B19 among pregnant women in the 5 countries. Belgium has the lowest estimated proportion of pregnant women susceptible to parvovirus B19 infection and the lowest associated force of infection. The risk of acquiring infection during pregnancy is significantly higher in Poland and Finland. This is also reflected in the ratio of maternal infections which varies from 1 in 643 pregnancies in Belgium to 1 in 171 pregnancies in Poland. Note that we are only able give a very broad estimate of the total number of fetal deaths due to parvovirus B19 infection during pregnancy because of the wide range of estimates reported in the literature for this parameter [1, 11].

Discussion

To our knowledge this study presents the first comprehensive epidemiological analysis of parvovirus B19 infections from large representative population-wide serum banks using a common laboratory assay in several European countries.

Our seroepidemiological study has revealed several previously unavailable interesting features of parvovirus B19 infection: while the age-specific seroprevalence profile in the four countries appear to follow broadly similar patterns (i.e. a rapid increase of seroprevalence in childhood, followed by a plateau in young adults and then another increase), we observed notable differences in the force of infection profiles in childhood and adolescence, as well as the risk of acquiring infection during pregnancy. Possible epidemiological explanations for the differences could include cultural and behavioural differences that lead to different contact rates in key transmission groups.

In addition of there being real country-specific epidemiological differences, our findings might have been influenced by the serological techniques used to measure parvovirus IgG exposure [12, 13]. In our pilot study, the diagnostic performance of the Mikrogen assay was very similar to the widely used Biotrin assay. Further the fact that antibody reactivity distributions obtained from different laboratories looked very similar suggests that inter-laboratory variation did not play a role in our findings. However, it is interesting to note that in all countries seroprevalence appeared to stay constant or decrease in very young children (less than 4 years of age), whereas one would expect it to increase following the loss of maternal antibodies in the first year of life. The reasons for this are unclear, but could include a lack of assay specificity for this age group exposed to many other viral agents including possibly the recently discovered human bocavirus belonging to the family *Parvoviridae* [14] .

As far as the differing force of infection profiles in childhood are concerned, there is a possibility that our estimates could have be influenced by the timing of the sample collection with respect to the epidemic pattern of parvovirus B19 infection, because these derivations

assume that the infection is in endemic equilibrium [15]. Figure 5 shows the recent yearly number of notified parvovirus B19 infection: for England and Wales the sera were collected two years after a very large outbreak in 1993, whereas the collection in Finland occurred just before a major outbreak; unfortunately no similar data are available for Belgium, Italy or Poland. It is possible that such “epidemic bias” could influence our findings such that force of infection estimates in Finland might have been larger if the sample collection had been carried out in 2002 after the epidemic. The Polish data are less sensitive to this ‘epidemic cycle’ bias because the serum samples were collected over a 9 year period and therefore the effects of epidemics are likely to have been averaged out. This could explain why the force of infection peak in Polish children is much wider than in other countries. Previous modeling studies have claimed that such timing bias has little influence on infectious disease parameters [15], but the authors based their findings on infections with shorter inter-epidemic periods than parvovirus B19. Other authors have also noted the interplay between timing of sample collection and epidemic cycles on seroprevalence [16].

While our estimates of seroprevalence in the age groups of child-bearing women are broadly similar to those found in other similar studies [10, 13, 17-19], our estimates of risk of maternal infection are generally smaller than those observed in other studies [6, 11, 17]. This could be due to the fact that our cross-sectional estimates are based on an average previous exposure, whereas other study designs could be potentially biased by the epidemic nature of parvovirus B19 transmission.

We have observed some major differences in risk of maternal infection in Europe. This discrepancy can be partly explained by higher rates of infection in children and teenagers (e.g. in Belgium, kindergarten attendance is very high from a young age), and, for Poland at least, a younger average maternal age. Our study shows that potentially greater proportions of maternal infection are expected in countries where pregnancy in teens is more prevalent (where susceptibility is markedly higher than in 20+ pregnant women).

Regardless of the differences observed between the countries, our study suggests that parvovirus B19 infection and its effects on maternal outcome are a poorly documented public

health issue in Europe. This is principally due to lack of collection of routine epidemiological data as occurs for most vaccine-preventable infections: indeed, parvovirus B19 infection is not a notifiable disease and only limited laboratory confirmation data are collected at national or European level, if at all. With an annual estimate of possibly up to 900 fetal deaths in the 5 countries studied, this could amount to an annual average of up to several thousand fetal losses when considering Europe as a whole. Exacerbated by the fact that the majority of fetal losses will occur during epidemics every 3-5 years, it is clear that enhanced surveillance of rash fever illness and laboratory notifications of parvovirus B19 infections in women of childbearing age would be necessary to obtain more accurate estimates of the overall burden of parvovirus B19 infection in the population.

This survey is to our knowledge the most comprehensive seroprevalence study of parvovirus B19 ever carried out in multiple European countries using a common laboratory methodology. Moreover, in conjunction with direct survey results on social contacts [20, 21], the current study will serve for basic parameterization of dynamic transmission models for close contact infectious diseases [22, 23]. Results from this study could also serve as an essential specific input in mathematical models evaluating the disease burden of parvovirus B19, as well as the effectiveness and cost-effectiveness of different parvovirus B19 vaccination strategies, in the event of a vaccine becoming available.

Acknowledgement

The authors are grateful to Veronik Hutse, Robert Vranckx (Scientific Institute of Public Health, Belgium) and Marcello Guido for carrying laboratory testing.

Declaration of interest

This study was financially supported by grant SP22-CT-2004-502084 of the FP7 programme of the European Commission, DG Research and the Flemish Fund for Scientific Research (FWO grant G.0393.04).

References

(1) Broliden K, Tolfvenstam T, Norbeck O. Clinical aspects of parvovirus B19 infection. *Journal of Internal Medicine* 2006; 260: 285-304.

(2) Tolfvenstam T*, et al.* Frequency of human parvovirus B19 infection in intrauterine fetal death. *Lancet* 2001; 357: 1494-1497.

(3) Isa A*, et al.* Prolonged activation of virus-specific CD8+T cells after acute B19 infection. *PLoS Medicine* 2005; 2: e343.

(4) Young NS, Brown KE. Parvovirus B19. *N Engl J Med* 2004; 350: 586-597.

(5) Zaaijer HL, Koppelman MH, Farrington CP. Parvovirus B19 viraemia in Dutch blood donors. *Epidemiology and Infection* 2004; 132: 1161-1166.

(6) Valeur-Jensen AK*, et al.* Risk factors for parvovirus B19 infection in pregnancy. *Journal of the American Medical Association* 1999; 281: 1099-1105.

(7) Ballou WR*, et al.* Safety and immunogenicity of a recombinant parvovirus B19 vaccine formulated with MF59C.1. *Journal of Infectious Diseases* 2003; 187: 675-678.

(8) Farrington CP. Modelling forces of infection for measles, mumps and rubella. *Statistics in Medicine* 1990; 9: 953-967.

(9) Shkedy Z*, et al.* Modeling the force of infection using monotone local polynomials. *J Roy Stat Soc, Ser C (Appl Stat)* 2003; 52: 469-485.

(10) Gay NJ*, et al.* Age specific antibody prevalence to parvovirus B19: how many women are infected in pregnancy? *Communicable disease report CDR review* 1994; 4: R104-107.

(11) van Gessel PH*, et al.* Incidence of parvovirus B19 infection among an unselected population of pregnant women in the Netherlands: A prospective study. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2006; 128: 46-49.

(12) Ferguson M, Heath A. Report of a collaborative study to calibrate the Second International Standard for parvovirus B19 antibody. *Biologicals* 2004; 32: 207-212.

(13) Kelly HA*, et al.* The age-specific prevalence of human parvovirus immunity in Victoria, Australia compared with other parts of the world. *Epidemiology and Infection* 2000; 124: 449-457.

(14) Manning A*, et al.* Epidemiological profile and clinical associations of human bocavirus and other human parvoviruses. *Journal of Infectious Diseases* 2006; 194: 1283-1290.

(15) Whitaker HJ, Farrington CP. Estimation of infectious disease parameters from serological survey data: the impact of regular epidemics. *Statistics in Medicine* 2004; 23: 2429-2443.

(16) Nascimento JP*, et al.* The prevalence of antibody to human parvovirus B19 in Rio de Janeiro, Brazil. *Revista do Instituto de Medicina Tropical de São Paulo* 1990; 32: 41-45.

(17) Koch WC, Adler SP. Human parvovirus B19 infections in women of childbearing age and within families. *Pediatric Infectious Diseases Journal* 1989; 8: 83-87.

(18) Alanen A*, et al.* Seroprevalence, incidence of prenatal infections and reliability of maternal history of varicella zoster virus, cytomegalovirus, herpes simplex virus and parvovirus B19 infection in South-Western Finland. *BJOG: an international journal of obstetrics and gynaecology* 2005; 112: 50-56.

(19) Enders M, Weidner A, Enders G. Current epidemiological aspects of human parvovirus B19 infection during pregnancy and childhood in the western part of Germany. *Epidemiology and Infection* 2006 1-7.

(20) Edmunds WJ, O'Callaghan CJ, Nokes DJ. Who mixes with whom? A method to determine the contact patterns of adults that may lead to the spread of airborne infections. *Proceedings Biological sciences / The Royal Society* 1997; 264: 949-957.

(21) Beutels P*, et al.* Social mixing patterns for transmission models of close contact infections: exploring self-evaluation and diary-based data collection through a web-based interface. *Epidemiology and Infection* 2006; 134: 1158-1166.

(22) Ferguson NM*, et al.* Strategies for mitigating an influenza pandemic. *Nature* 2006; 442: 448-452.

(23) Wallinga J, Teunis P, Kretzschmar M. Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents. *American Journal of Epidemiology* 2006; 164: 936-944.

(24) Miller E*, et al.* Immediate and long term outcome of human parvovirus B19 infection in pregnancy. *British Journal of Obstetrics and Gynaecology* 1998; 105: 174-178.

	Year of collection	sample size	Age range	Number of equivocal results
Belgium	2001-2003	3098	0-82	18
England & Wales	1996	2836	1-79	14
Finland	1997-1998	2500	1-79	1
Italy	2003-2004	2515	1-79	1
Poland	1995-2004	2500	1-79	5

Table 1: Characteristics of serum banks used in our study.

	Belgium	England & Wales	Finland	Italy	Poland
Number of live births in 1997	116210	726696	59329	534461	412634
Estimated proportion of susceptible pregnant women (95% CI)[1]	26.0% (23.5%-28.3%)	38.1% (35.1%-41.2%)	43.5% (40.1%-46.9%)	39.9% (36.6%-43.0%)	36.8% (33.8%-40.1%)
Risk of acquiring parvovirus B19 infection during pregnancy in susceptible women (95% CI) [1]	0.61% (0.12%-1.37%)	0.69% (0.17%-1.24%)	1.24% (0.76%-1.86%)	0.92% (0.52%-1.41%)	1.58% (1.03%-2.18%)
Estimated number of parvovirus B19 infections occurring in pregnant women (95% CI) [1]	180 (34-372)	1886 (478-3160)	318 (208-440)	1952 (1179-2738)	2411 (1712-3047)
Rate of pregnancies with parvovirus B19 infection (95% CI) [1]	1 in 643 (312-3330)	1 in 386 (229-1518)	1 in 186 (134-284)	1 in 273 (195-453)	1 in 171 (135-240)
Estimated yearly average number of fetal losses due to parvovirus B19 infection (low-high)[2]	1-18	19-189	3-32	20-195	24-241

Table 2: Estimated burden of pregnancy-related parvovirus B19 infection in 5 European countries

[1] Based on local quadratic model results

[2] The overall risk of fetal loss due to parvovirus B19 infection is controversial. Reports in the literature vary from 0% [11] to 9% [24] of maternal infections. For simplicity, we have assumed a low and high rate of 1% and 10%, respectively.

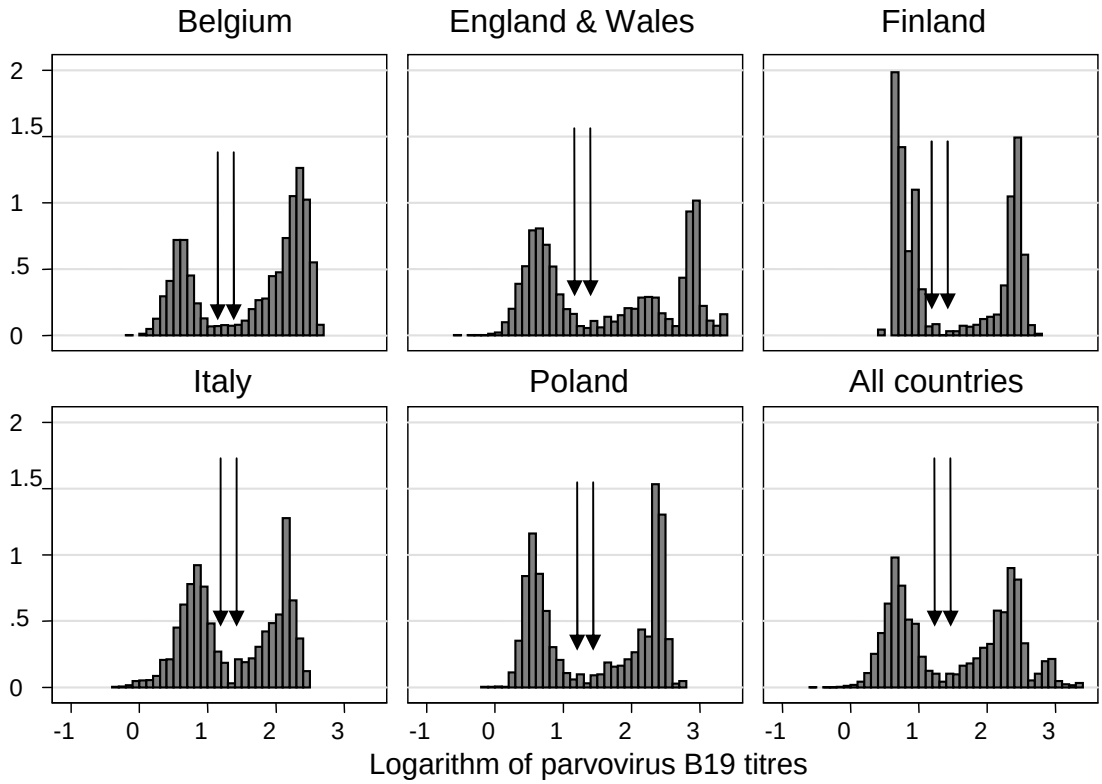

Belgium
England & Wales
Finland
Italy
Poland
All countries
2
1.5
1
.5
0
-1
0
1
2
3
Logarithm of parvovirus B19 titres

Figure 1

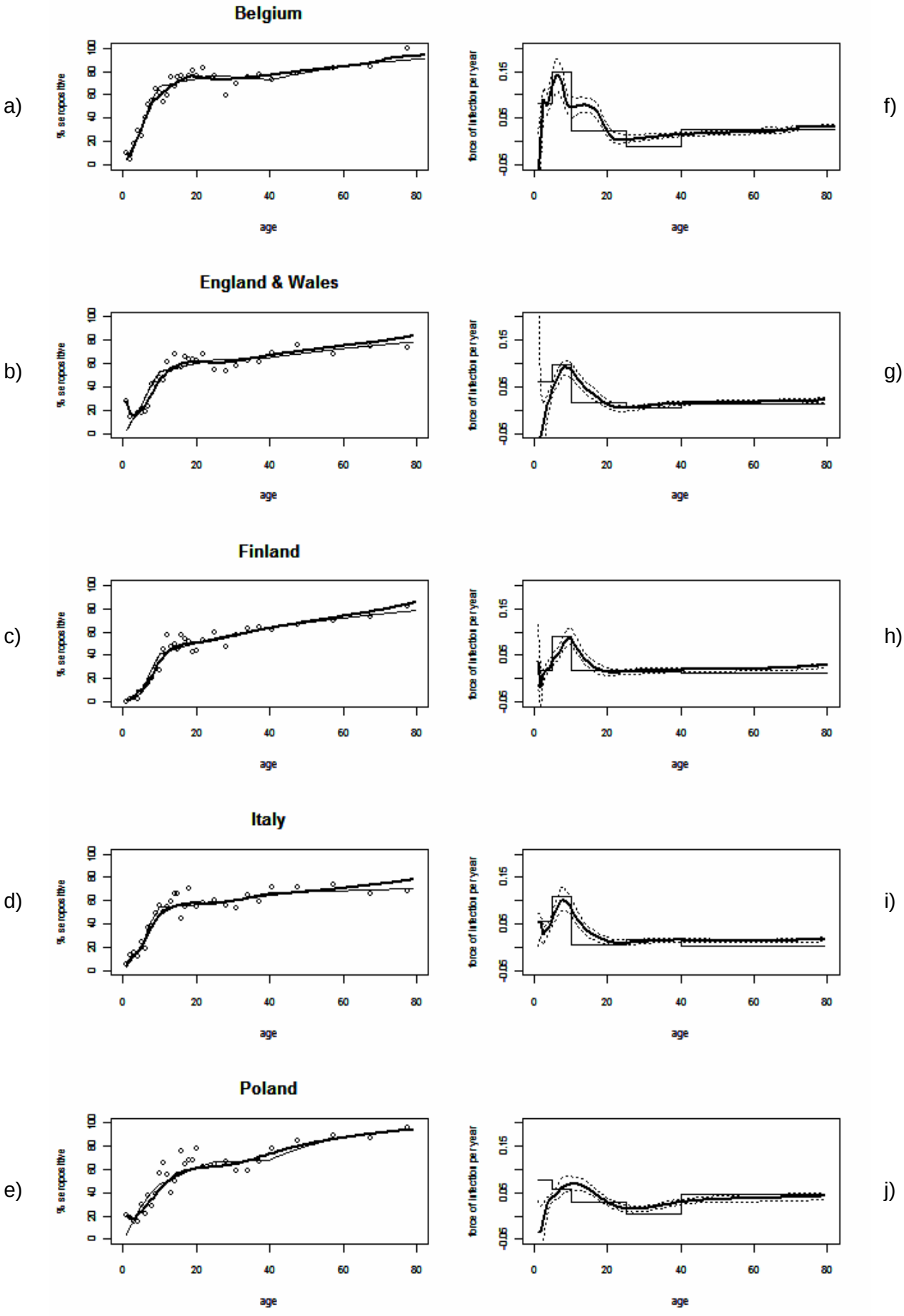
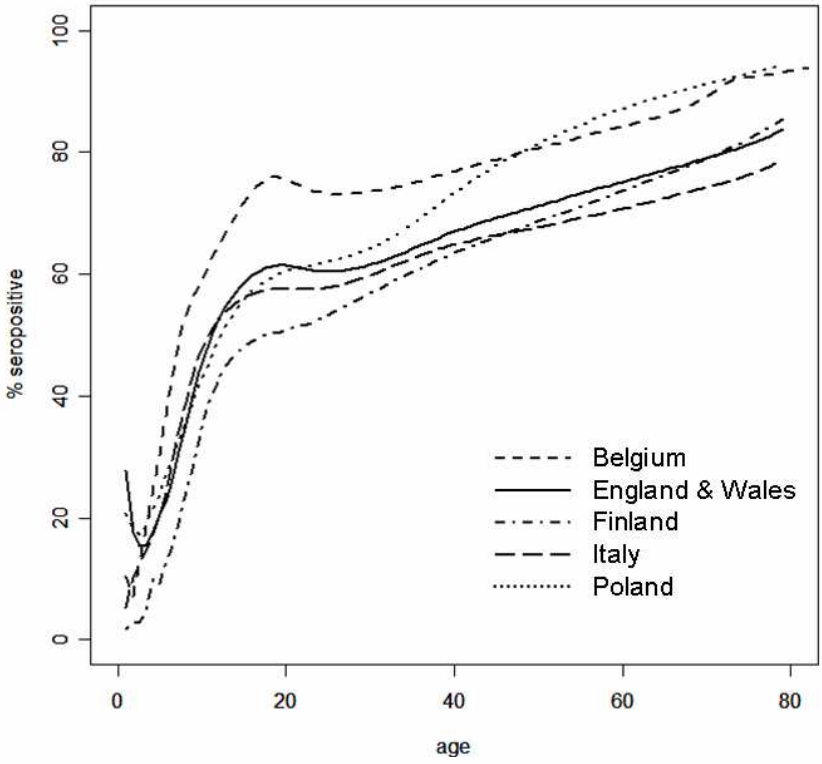

a)
Belgium
% seropositive
age
f)
force of infection per year
b)
England & Wales
g)
c)
Finland
h)
d)
Italy
i)
e)
Poland
j)

Figure 2

a)


% seropositive
0
20
40
60
80
100
0
20
40
60
80
age
Belgium
England & Wales
Finland
Italy
Poland

b)

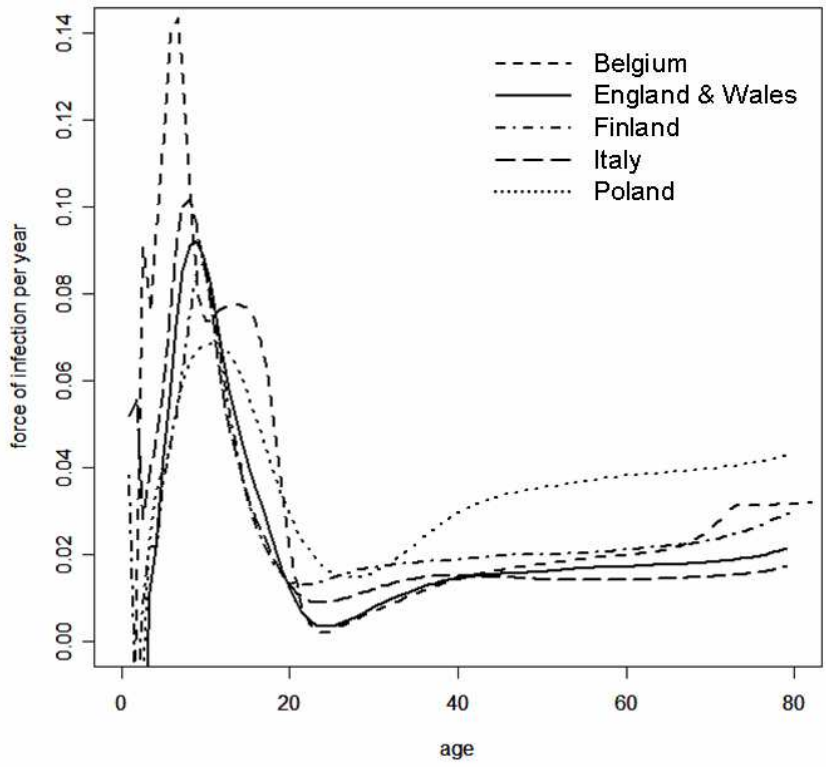

force of infection per year
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0.14
0
20
40
60
80
age
Belgium
England & Wales
Finland
Italy
Poland

Figure 3

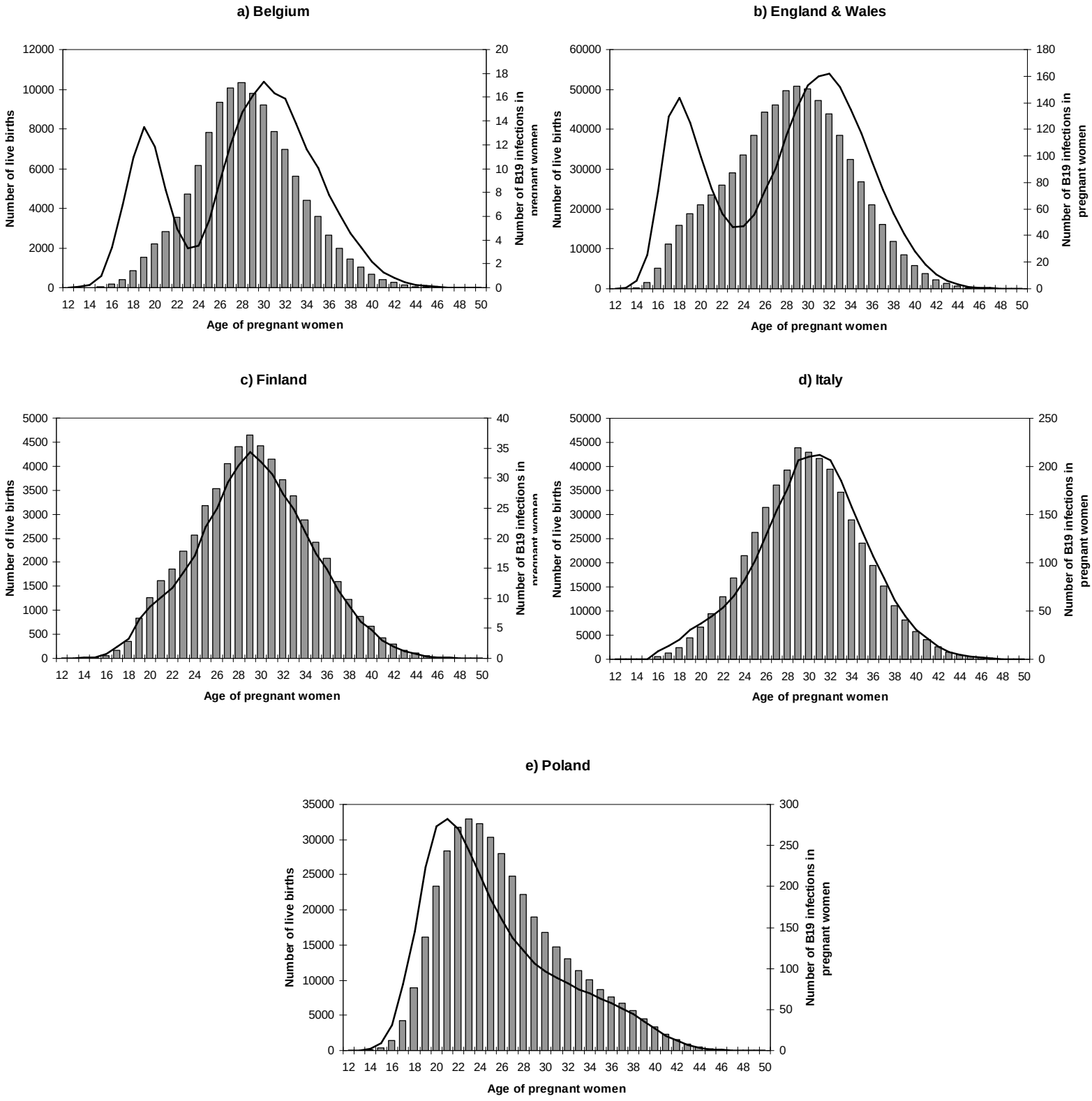
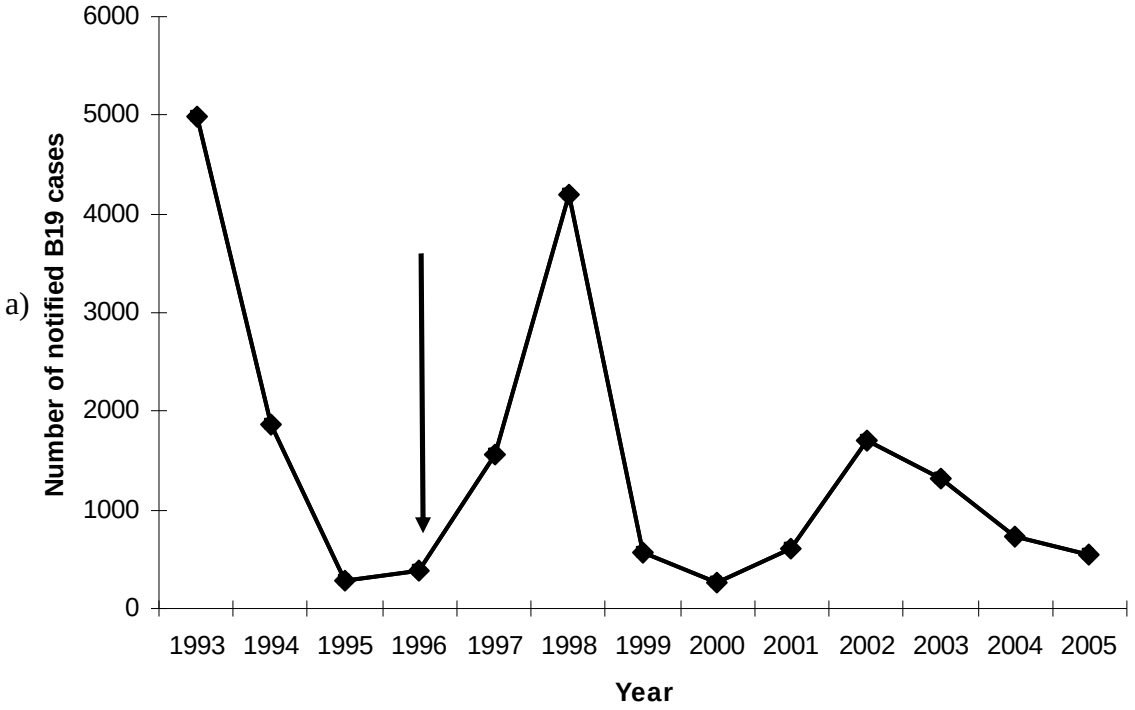

a) Belgium
Number of live births
Number of B19 infections in pregnant women
Age of pregnant women
b) England & Wales
Number of live births
Number of B19 infections in pregnant women
Age of pregnant women
c) Finland
Number of live births
Number of B19 infections in pregnant women
Age of pregnant women
d) Italy
Number of live births
Number of B19 infections in pregnant women
Age of pregnant women
e) Poland
Number of live births
Number of B19 infections in pregnant women
Age of pregnant women

Figure 4


a)
Number of notified B19 cases
6000
5000
4000
3000
2000
1000
0
1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005
Year

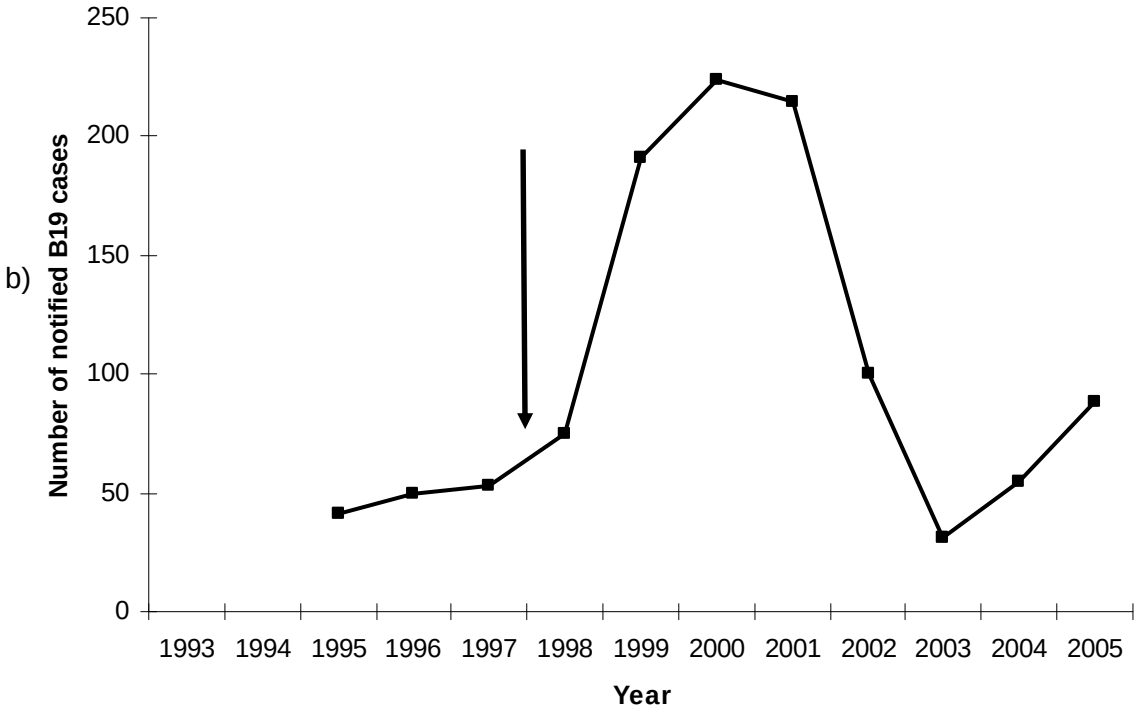

b)
Number of notified B19 cases
250
200
150
100
50
0
1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005
Year

Figure 5

Figure 1: Histograms of log parvovirus B19 antibody reaction level distribution of national serum banks in 5 countries. Left and right arrows indicate negative and positive cutoffs, respectively, as indicated by the manufacturer.

Figure 2: Parts a), b) c) d) e) show different estimates of parvovirus B19 seroprevalence profiles in Belgium, England and Wales, Finland, Italy and Poland, respectively. The circles indicate point estimates for each age group, the thick line indicates the local quadratic model and the thin line indicates the piece-wise constant model. Parts f), g), h), i) and j) show the force of infection estimates corresponding to the seroprevalence profiles in a), b), c), d) and e), respectively. The thick line indicates the local quadratic model, the dotted line represents 95% confidence intervals of the local quadratic and the thin line the piece-wise constant model.

Figure 3: a) Comparison of age-specific parvovirus B19 seroprevalence profiles in Belgium (short-dashed line), England & Wales (continuous line), Finland (dashed–dot line), Italy (long-dashed line) and Poland (dotted line) estimated using the local quadratic model; b) Comparison of age-specific parvovirus B19 force of infection estimates from the local quadratic model in Belgium (short-dashed line), England & Wales (continuous line), Finland (dashed–dot line), Italy (long-dashed line) and Poland (dotted line).

Figure 4: Distribution of life births by age of the mother in 1997 (shown in bars, y-axis on the left) according to Eurostat and distribution by age of yearly estimated number of B19 infections occurring during pregnancy based on the local quadratic model of seroprevalence and force of infection (line, y-axis on the right).

Figure 5: Incidence of notified B19 infections in England and Wales a) and in Finland b). Arrows indicate timing of sera collection.