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PREVENTION OF CONGENITAL AND PERINATAL INFECTIONS

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Perinatal and congenital infections cause morbidity and mortality throughout the world. While there are a large number of pathogens that can occasionally be harmful for the unborn child, some are of considerable public health impact, for example rubella, varicella, syphilis, hepatitis B, toxoplasmosis, or infections with cytomegalovirus (CMV) or human immunodeficiency virus (HIV). The advances in the field of clinical microbiology have increased our options in terms of preventive strategies, early diagnosis, clinical interventions and therapeutic alternatives to combat these infections.

When a considerable public health impact of a given infection is evident, preventive measures can be discussed in relation to the epidemiology, the available resources and the acceptance in the population. Information on hygienic measures and other means to avoid infection is another cornerstone in the preventive work. Immunisation before pregnancy is an option for rubella, hepatitis B and varicella. In cases where intervention to prevent damage to the unborn child is possible, large screening programmes can be organised in order to identify maternal infections that may otherwise not be recognised due to uncharacteristic or subclinical symptoms. Congenital syphilis can be prevented by antibiotic treatment in early pregnancy, transmission of HIV by antiviral treatment of mother and newborn, and transmission of hepatitis B by vaccination and immunoglobulin treatment of the newborn. Identification of a neonate with congenital CMV infection or toxoplasmosis allows treatment to reduce harm.

Lack of resources and appropriate maternal care stand in the way of efficient programmes, but there is also a need of increased knowledge. Many of these interventions could be improved not only by a better understanding of the epidemiology and the impact of the diseases as well as further research into improved diagnostics and treatments and development of vaccines, but also by distribution of information to pregnant women and health care professionals. This issue of Eurosurveillance is dedicated to infectious diseases and pregnancy and contains a number of articles highlighting different aspects of the epidemiology and control and prevention efforts for diseases such as toxoplasmosis, rubella, varicella, sexually transmitted diseases e.g. HIV and hepatitis B, and cytomegalovirus infections.

Safe vaccines against, for example, rubella, exist and are very efficient in preventing infection in the mother [1]. It is clear that congenital rubella can be eradicated by vaccination programmes, a goal that has already been reached in the Scandinavian countries and the United States (US). The combination of high uptake two-dose

childhood vaccination programmes in combination with postpartum vaccination of susceptible women has eliminated rubella within a decade [1-3]. Whatever the strategy –adherence and efficacy of the programmes will be decisive for the end result. This is clearly illustrated in an article in this issue by Pandolfi and co-workers that gives an overview of data from surveillance systems of the World Health Organization (WHO) and the European surveillance community network for vaccine-preventable infectious diseases, EUVAC-NET [4]: rubella still circulates in many parts of the world, including Europe. And not only in countries in which programmes for rubella elimination have only recently been implemented, but also in countries with a long history of vaccination with low uptake of the vaccine such as Italy. The authors review different strategies to improve the situation with the goal to achieve not only herd immunity but also protection of all women of childbearing age as long as the global circulation cannot be stopped. They further propose to include varicella vaccine in such programmes in order to prevent varicella in pregnancy, which bears a risk for foetal embryopathy and neonatal disease [5]. A vaccine against varicella has been available for a long time, and has been employed in universal childhood vaccination for example in the US since 1995 [6]. However, only few countries in Europe, e.g. Germany, have so far followed the US example. It is, however, likely that more countries will introduce this vaccine as combination vaccines become more available, which implies a considerable reduction in the costs. As the authors point out, the use of the vaccine for the prevention of adult varicella is today suboptimal. Wherever possible, the vaccine should be offered to non-pregnant women of childbearing age who do not have acceptable evidence of previous infection (susceptibility should preferentially be confirmed by immunity testing), especially women working as carers for children and adolescents, and parents of young children.

Vaccines may also be used in newborns in order to protect against maternal transmission during birth, as is the case for hepatitis B [7]. If vaccination is not possible such as for syphilis and infections with human immunodeficiency virus (HIV), transmission of the infection to the child may be prevented by antimicrobial therapy of the mother [8,9]. The cornerstone for such programmes is testing pregnant women when they have their first contact with maternity care. Surveillance of the efficiency of the preventive programmes is crucial for their success. As described by Giraudon et al., an efficient surveillance programme has been in place in London for nearly ten years, which monitors the extent of antenatal testing and the prevalence of susceptibility to HIV infection, hepatitis B, syphilis and rubella [10]. If the acceptance rate for testing is low, this will be investigated rapidly and the information used

promptly to improve the uptake. It is noteworthy that this study also investigated how children of women infected with hepatitis B are followed up by vaccination, a programme that frequently suffers from a high rate of non-adherence.

A more cumbersome strategy has to be adopted if treatment needs to be given to the mother within a short interval after contracting the infection, in order to prevent permanent damage of the child. This is the case with *Toxoplasma gondii* infections, and seronegative women, who may be exposed any time, have to be screened at monthly intervals starting at the latest in the 12th week of pregnancy [11]. C. Cornu et al. studied factors influencing adherence to such a programme in the French Rhone-Alps region [12]. The authors conclude that there are gaps in the adherence to the screening schedule, regarding the adequate time of first visit, intervals between visits and numbers of subsequent visits for sampling. They suggest that simplification of the logistics of the procedure (prescription, reimbursement) might improve adherence, but also point out that special attention needs to be paid to the background of the women who are not able to follow the schedule.

A study from Greece by I. Elefsiniotis et al. highlights the, often significant, differences in the epidemiology of hepatitis B that exist between immigrants and indigenous inhabitants [13]. The very high rate of hepatitis B in immigrants from Albania illustrates the well-known fact that special attention has to be taken to include immigrants and refugees in ongoing public health programmes.

Other populations who need special attention and care are drug users who are at high risk of contracting blood borne and sexually transmitted disease. These aspects and the need for social and psychiatric support is well summarised in the review from Lisbon by V.A. Gyarmathy and co-workers [14].

The present status and knowledge of congenital CMV is the topic of three more papers in this issue of Eurosurveillance. The fact that CMV infections are without symptoms in pregnant women and in most of the congenitally infected neonates, has made the exploration of the topic cumbersome, but much information has been gained from large prospective studies (see the review by Ludwig and Hengel [15]). Previously, retrospective diagnosis of congenital CMV at the time of the appearance of late sequelae had not been possible as differentiation between congenital and the very frequent early postnatal infection could not be done. However, advances in molecular diagnostics now allow a retrospective diagnosis, provided that dried blood spots from metabolic testing are preserved, which at the same time provide an easier approach to epidemiological investigations, as exemplified by P. Paixão et al. [16].

The epidemiology of CMV varies widely in different populations but, wherever tested to date, congenital CMV is a major cause (20-25 %) of severe neurologic deafness, often with delayed onset. Severe neurologic disability and ocular problems may also occur. The present knowledge on congenital CMV infection is summarised in the review by A. Ludwig and H. Hengel [15] and the report by A. Vossen et al. [17] from the International Conference on Congenital CMV, held at the Centers for Disease Control and Prevention (CDC) in Atlanta in November 2008.

A first-grade conference on this topic being held at the US CDC underlines the great efforts directed to the prevention of congenital

CMV in the US. The development of a CMV vaccine is considered a first priority, followed by seroepidemiology in different populations and mapping of the extent of congenital CMV among deaf children, pathophysiology and many other aspects.

In Europe, a screening programme to identify primary CMV infection in pregnancy has been in place for some years in Italy, now withdrawn but considerable voluntary testing is still ongoing, and valuable experience has been gained [18-19]. Several other projects are ongoing or starting (e.g. in Belgium, France, Germany, Sweden, the United Kingdom and several other European countries). Controlled studies are being initiated on the effectiveness of immunotherapy in preventing or alleviating foetal damage and on antiviral therapy for the treatment of children with symptoms affecting the central nervous system [20].

There is also a role for hygienic measures in avoiding transmission of CMV, a ubiquitous infection among young children. The European Congenital CMV Initiative (ECCI), a collaborative organisation of European CMV researchers from many disciplines, initiated by G.M. Revello, T. Lazarotto and M. Barbi is now distributing information to the public and to health professionals through the London-based website (www.ecci.ac.uk). The website also contains a case register. Further information is available at the website of the US CDC (www.cdc.gov/cmvm) as well as on a national basis on a Swedish website on congenital-perinatal infection (www.infpreg.se). As it is apparent that the public health impact of congenital CMV damage is considerable, more resources are now needed in Europe as in the US in order to make further progress in prevention. The strength of a European collaboration has previously been well illustrated in the European Union collaborative study of mother-to-child transmission of HIV, hepatitis C and toxoplasmosis [21-23]

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SURVEILLANCE FOR HEPATITIS B VIRUS INFECTION IN PREGNANT WOMEN IN GREECE SHOWS HIGH RATES OF CHRONIC INFECTION AMONG IMMIGRANTS AND LOW VACCINATION-INDUCED PROTECTION RATES: PRELIMINARY RESULTS OF A SINGLE CENTER STUDY

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Epidemiological data on the prevalence of serological markers of hepatitis B virus (HBV) infection in pregnant women in Greece are limited. We evaluated the prevalence of HBV serological markers in a multinational population of pregnant women in Athens, Greece. The overall prevalence of hepatitis B surface antigen (HBsAg) was 4.1% with the highest rates among Albanian immigrants (12%). Relatively low vaccination-induced protection rates (32.5%) were observed, a finding suggesting that surveillance and immunisation programmes targeted at pregnant women are necessary.

Background

Worldwide, about 350 million people are chronically infected with hepatitis B virus (HBV). Vertical (mother-to-infant) transmission of the infection occurs usually in perinatal period and is responsible for the majority of the disease burden in endemic areas. The risk of vertical transmission generally depends on the level of maternal infectivity during pregnancy, i.e. the presence of hepatitis B e-antigen (HBeAg) or HBV DNA levels [1,2].

Hepatitis B has long been a serious public health problem in Greece. Historically, Greece used to have the highest burden of HBV infection in the European Union, and an early hepatitis B prevention programme introduced in 1982 and aimed at high-risk groups had had little impact on disease incidence or prevalence [3]. More recent HBV vaccination programmes, demographic and socioeconomic changes, safer medical and nursing practices and screening of blood donors have resulted in a significant decline in chronic HBV infection in our country in the past decade [3,4]. However, the arrival of a great number of refugees, especially from countries with endemic HBV infection, is likely to have influenced this trend, requiring a reevaluation of epidemiological data. To date, epidemiological data on the prevalence of serological markers of HBV infection in pregnant women in Greece have been limited [5].

HBV prevalence in pregnant women

In our study we examined the current prevalence of HBV serological markers in a multinational population of pregnant

women in Athens, Greece. Between September 2008 and December 2008 a total of 749 pregnant women (mean age 28.5 years) who gave birth at the Department of Obstetric and Gynaecology of the Maternal and Perinatal Hospital 'Elena Venizelou' of Athens were prospectively evaluated. Hepatitis B surface antigen (HBsAg), hepatitis B e-antigen (HBeAg), antibody to hepatitis B e-antigen (anti-HBe), antibody to hepatitis B core antigen (anti-HBc) and antibody to hepatitis B surface antigen (anti-HBs) were detected using routine commercially available enzyme immunoassays (Abbott Laboratories, Abbott Park, Illinois, US). All women in the study population were screened for HBsAg, anti-HBc and anti-HBs, whereas HBeAg and anti-HBe were evaluated only in those who tested positive for HBsAg [HBsAg(+)].

The study was performed in accordance with the Helsinki Declaration and was reviewed and approved by the Hospital Ethics Committee.

Almost half of the study population was originally from Greece (370/749, 49.4%), 29% came from Albania (217/749), 12.8% (96/749) from Eastern European countries (Russia, Romania, Bulgaria), 5.2% (39/749) from Asian countries (Philippines, India and China) and 3.6% (27/749) from African countries (Egypt, Nigeria, Kenya). The place of origin of each woman included in the study population was determined on the basis of her and/or her parents' birth place (in case of second generation immigration), according to the medical records data. The proportion of each group in the study population is presented in Figure 1. It is important to note the small proportion of women from Asia and Africa in our study population and that the majority of these came from countries with intermediate HBV prevalence.

Overall, 4.1% (31/749) of women were HBsAg(+) and the vast majority of them (26/31, 83.87%) were Albanian. The prevalence of HBV serological markers in the study population, according to the place of origin, is presented in Figure 2. Among Albanian women the prevalence of HBsAg was 12% followed by 2.1% among women from Eastern European countries. The prevalence of HBsAg

among women of Greek origin (0.8%) was very low and significantly lower in comparison with the mean value of the studied population ($p < 0.001$). It is important to note that none of the women from countries of Asia and Africa were HBsAg(+). A significant proportion of young women from Asia and Africa who live and work in Greece are second generation immigrants and the majority of them were born in our country, in contrast to Albanian or Eastern European women. Moreover, as previously noticed, the majority of Asian and African women of our study population were from countries with intermediate HBV prevalence. Both factors could explain the discrepancy between the levels of HBV serological markers among Asian/African and Albanian/Eastern European women, in our study.

Overall, only 1.4% of HBsAg(+) women were also HBeAg(+) whereas the vast majority (98.6%) were HBeAg(-)/antiHBe(+). Despite that, it is well known that a significant proportion of HBeAg(-) chronic HBV infected women in our country exhibit high levels of viremia during the perinatal period, especially due to precore mutation of the HBV genome [6]. More than half (57.1%) of the Albanian women exhibited anti-HBc seropositivity followed by Eastern European women (28.1%), Asian women (17.9%) and African women (11.1%) whereas only 5.1% of Greek women presented serological markers of previous HBV exposure. Moreover, serological markers of past HBV infection with spontaneous recovery [antiHBc(+) and antiHBs(+)] were observed in 15.2% of the whole study population whereas 32.5% exhibited vaccination-induced protection [characterised by the presence of isolated antiHBs(+)].

Importantly, vaccination-induced protection rates were relatively highest and comparable among Albanian and Greek women (40.3% vs 33.8% respectively, $p = 0.115$) whereas significantly lower rates were found among Eastern European (22.9%), Asian (15.4%) and African (11.1%) women ($p < 0.05$, in all comparisons).

Conclusion

In the study described in this paper the overall prevalence of HBsAg among pregnant women in Greece was estimated to be 4.1% with highest rates among Albanian immigrants (12%). The HBeAg(-)/antiHBe(-) serological status was observed in the vast majority of HBsAg(+) women in our study population. Relatively low vaccination-induced protection rates (32.5%) were observed, a finding suggesting that surveillance and immunisation programmes targeted at pregnant women are necessary in order to avoid vertical transmission of HBV infection.

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FIGURE 1

Study on prevalence of serological markers of hepatitis B virus infection among pregnant women in Greece - distribution of the study population by place of origin (n=749)

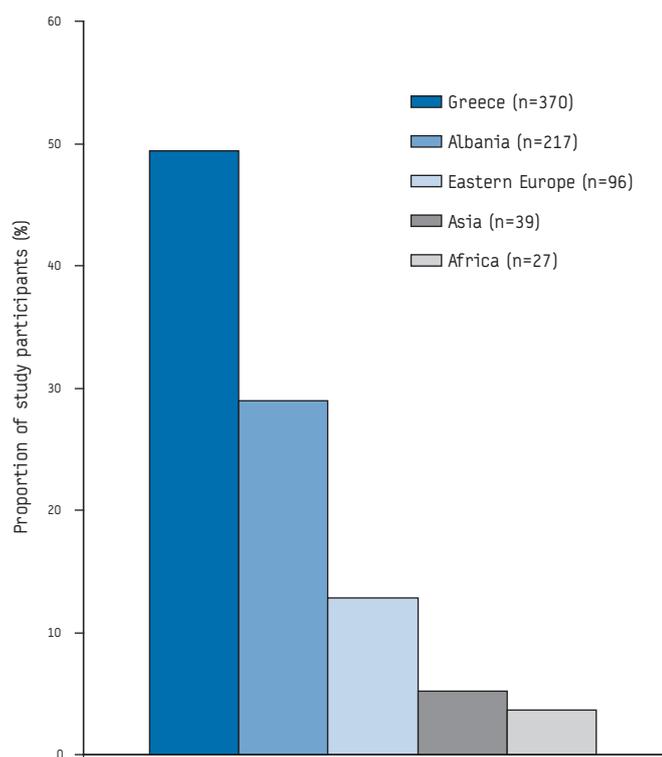
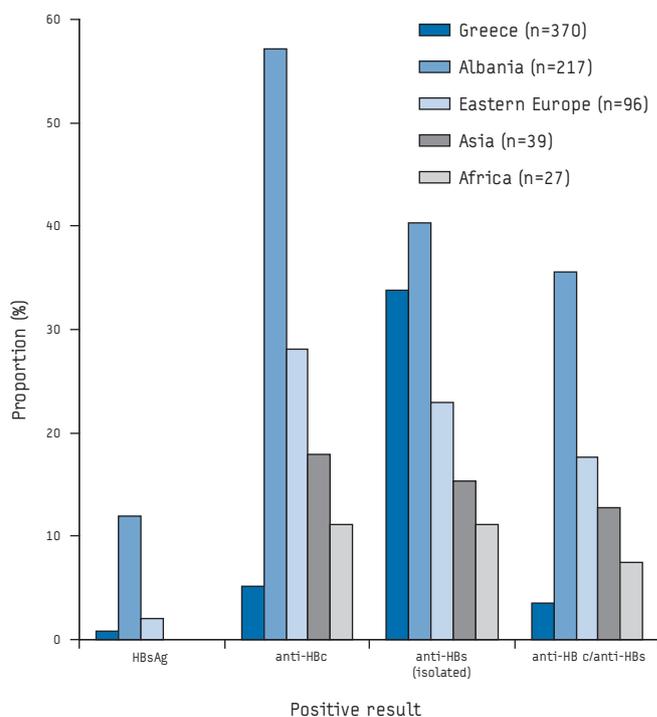


FIGURE 2

Prevalence of serological markers of hepatitis B virus infection among pregnant women in Greece, according to their place of origin (n=749)



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ANTENATAL SCREENING AND PREVALENCE OF INFECTION: SURVEILLANCE IN LONDON, 2000-2007

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In the United Kingdom (UK), it is recommended to universally offer antenatal infection screening for human immunodeficiency virus (HIV), hepatitis B and syphilis infections, and susceptibility to rubella for the benefit of the mother and to reduce vertical transmission of infection. This paper describes the surveillance of antenatal infection including uptake of screening, and the results of testing in pregnant women in London between 2000 and 2007. Antenatal screening coordinators in liaison with midwifery heads and microbiologists at all thirty London National Health Service (NHS) Trust maternity units supplied quarterly data on the number of pregnant women booked for antenatal care, tests done, and tests results. The overall estimated uptake of screening increased since 2000 and reached 95.6% for HIV, 96.5% for syphilis, 96.2% for hepatitis B and 97% for rubella susceptibility by the second half of 2007. There is considerable variation in the performance between NHS Trusts. The overall estimated prevalence of HIV infection was 3.4/1,000 women (ranging from <1/1,000 to 10/1,000 across Trusts), of hepatitis B (HBsAg-positive) was 11.3/1,000 (2.6/1,000- 23.9/1,000), of syphilis was 4.4/1,000 (<1/1,000-16.3/1,000) and of rubella susceptibility was 39.3/1,000 (19-103/1,000). Antenatal infection screening has improved and there has been some success in implementation of national policy. However, screening uptake and prevalence of infection vary considerably across London NHS Trusts and some women are evidently disadvantaged. Improvements in information systems should help local partners to focus their interventions in those Trusts where work is still needed to increase testing as well as the capacity to monitor the uptake of screening.

Introduction

Universal antenatal infection screening aims to identify infection early so that mothers can be offered advice and interventions in pregnancy and afterwards for their own health benefit as well as to reduce the chance of vertical transmission. In 1998 in the United Kingdom (UK), the Department of Health recommended that all pregnant women should be offered antenatal screening for hepatitis B infection [1]. In 1999, UK national policy stated that all pregnant women should be offered and recommended testing for human immunodeficiency virus (HIV) infection, along with other antenatal screening tests, as an integral part of their antenatal care, and that this offer as well as the patient's decision to undergo the testing should be recorded [2]. National guidelines also require robust systems to monitor the uptake of testing. In 2003, the

Department of Health reinforced the policy by publishing a set of antenatal screening standards including those for syphilis infection and susceptibility to rubella virus infection [3].

In 2007, there were an estimated 77,400 people living with HIV in the UK, of whom over a quarter (28%) were unaware of their infection. Almost half (48%) of those individuals who had been diagnosed were resident in London [4]. Antenatal Infection Screening Surveillance (AISS) was implemented in London in 2000 in collaboration with the National Health Service (NHS) in London, by the then Regional Epidemiology Services of the Public Health Laboratory Service now the Health Protection Agency (HPA) [5]. It monitors the implementation of the national screening policy in London NHS Trusts (i.e. public hospitals), as well as the antenatal prevalence of HIV, hepatitis B and syphilis infections, and susceptibility to rubella. The results are reported quarterly to NHS Trusts and health authorities, to assist them in understanding the infection burden among pregnant women and to facilitate targeting of interventions where needed in London.

This article describes the AISS system as well as the gradual increase in antenatal infection screening during 2000 to 2007 and prevalence of infection in pregnant women reported at NHS Trusts across London.

Methods

The surveillance system was developed throughout London in collaboration with 30 maternity units in 28 NHS Trusts (two of the Trusts comprising of two maternity units). In each Trust, the head midwife of the maternity unit and the antenatal screening coordinator liaise with the microbiologists to obtain the information and provide it to the HPA. Currently 96% of births take place in obstetric units in hospital, and these Trusts are estimated to cover the large majority of the birth cohort (around 115,000 births per year in London) [6]. Staff at each Trust return a six-monthly (since 2005 quarterly) form to the HPA London regional office. Forms include source of information, aggregated data for the total number of pregnant women registered for antenatal care (hereafter called "booked" for antenatal care), tests carried out for HIV, hepatitis B, syphilis and rubella antibody, and the total number of positive tests. Positive tests are defined as HIV antibody positive, hepatitis B surface antigen (HBsAg) positive, syphilis positive with enzyme immunoassay test and rubella antibody <10 iu/ml.

The uptake of screening for each infection was estimated by calculating the proportion of tests done per total number of women booking for antenatal care. Prevalence of infection was calculated as the total number of positive tests per 1,000 tests done.

Results

By the end of June 2008, all 30 maternity units at the 28 London NHS Trusts had returned completed forms for the years 2000 to 2007. In 2006 and 2007, reports were received for all four quarters from all Trusts. There were some gaps in information provided by individual units, but all Trusts participated in the scheme.

Uptake of screening

Estimated uptake of antenatal screening in 2007 was 96.4% for hepatitis B, 96.6% for syphilis and 96.8% for rubella susceptibility. HIV screening uptake, which had been less than 70% in 2000, rose to an estimate of 95.1% in 2007 (Figure 1). Nevertheless, in 2007, valid quarterly reports where information on booking for antenatal care and test was given (108/112 reports) indicated that for at least 6,744 out of 138,618 booked women no HIV testing was reported. Based on average prevalence of antenatal

FIGURE 1

Uptake of antenatal screening for HIV, hepatitis B and syphilis; Health Protection Agency Antenatal Infection Screening Surveillance, London, half-years 2000-2007

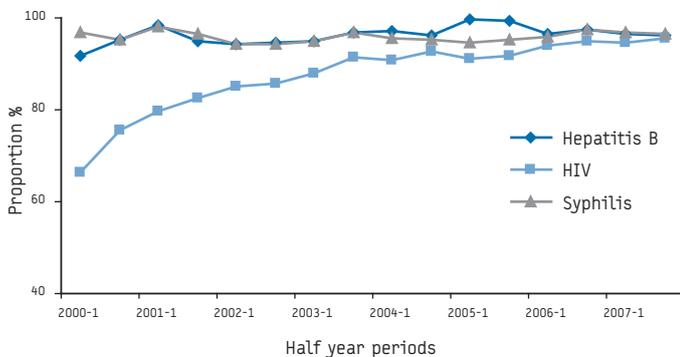
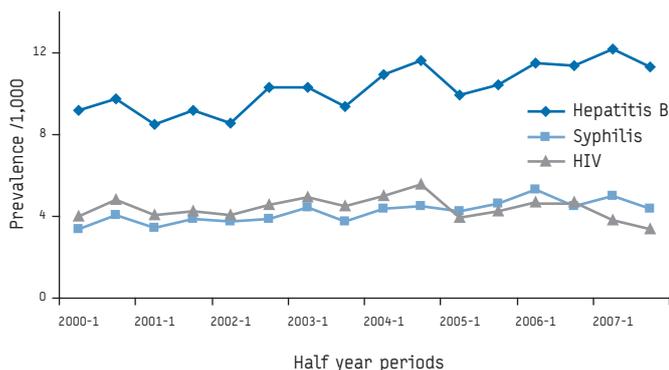


FIGURE 2

Prevalence of HIV, hepatitis B and syphilis; Health Protection Agency Antenatal Infection Screening Surveillance, London, half years 2000-2007



HIV infection in London as obtained through the AISS in 2007 (3.6/1,000), we estimated that around 24 babies were potentially at risk of vertical transmission of HIV and remained unrecognised. Three Trusts reported that in at least one quarter in 2007 less than 4/5 women had been screened for HIV.

Prevalence of infection

In 2007, the estimated overall prevalence of HIV infection, slightly decreasing, was 3.6/1,000 varying across Trusts (<1/1,000 to 10/1,000), of hepatitis B (HBsAg-positive) was 11.7/1,000 (3/1,000 to 24/1,000) and of syphilis was 4.7/1,000 (<1/1,000 to 16/1,000) (Figure 2). Prevalence of rubella susceptibility was 41/1000 (16/1,000 to 78/1,000) in 2007, compared to previous estimates of 37/1000 in 2001 and 34/1000 in 2004.

The prevalence of antenatal infection varies considerably across London's NHS Trusts (Table) and sectors ("pre 2006 NHS reorganization" London Strategic Health Authorities). HIV prevalence in 2007, ranged from 1.6/1,000 pregnant women in the North West London sector to 4.9/1,000 in the South East London sector, and was 50-fold higher at the NHS Trust with the highest prevalence compared to the one with the lowest prevalence (range from 0.2/1,000 to 10.1/1,000). For hepatitis B, the disparity was 11-fold (2.6/1,000 compared to 23.9/1,000), and for syphilis prevalence was 81-fold higher at the Trust most affected (range 0.2/1,000 to 16.3/1,000).

Data source, participation and data provided

In 2007, the source of information was missing from only two reports. Sources of data were derived from maternity and laboratory records such as manual records, delivery figures (birth register), electronic patient records, range of laboratory and maternity computer systems including Euroking K2, Winpath and Telepath. Only one Trust was unable to provide information about the number of bookings made. All Trusts were able to supply information on the number of screening tests performed apart from one Trust that did not provide syphilis data. All Trusts provided their positive results apart one that did not provide syphilis data and one unable to provide rubella data for two quarters.

Discussion

Overall in London, antenatal infection screening has improved and the implementation of the national policy can be regarded as a success to some degree. However, screening uptake and prevalence of infection does vary considerably across London NHS Trusts, and it is likely that in some pregnant women HIV infection remains undiagnosed thus putting unborn babies at risk of vertical transmission. Many NHS Trusts in London serve a population with high levels of HIV infections. This reflects the demography of the capital, with areas where a high proportion of women come from high prevalence countries. In 2006, overall 53% of women who gave birth in London had been born outside of the UK. In the same year, the prevalence of HIV among women born in sub-Saharan Africa who gave birth in the UK was 25/1,000 [4]. Though certain groups are at higher risk, it is essential that all women in London can benefit from early diagnosis and interventions to prevent their infants from becoming infected.

There were some problems with data completeness in some Trusts and thus there are limitations to the system. However, we believe that its overall results and conclusions are sound.

It is possible that some women reportedly not tested in the current pregnancy may have been tested prior to pregnancy [7]. Irrespective of this, they should be screened in the current pregnancy. An underestimation of screening uptake could also result if women booked for testing had pregnancy loss before being tested. However, screening uptake could also be overestimated, with tests repeated during pregnancy, or reported for women who had miscarried or women who were not booked, typically because they presented very late in the pregnancy. Detailed local audit would be necessary to accurately assess to what extent low uptake reported in some Trusts may reflect limitations in the reporting system. Exploration of this and further review at Trusts level is recommended along with an assessment of characteristics of women who were not screened. Those who decline screening may constitute a particular risk group and may have higher prevalence of HIV or other infections [8]. Variability in the monitoring systems in place may make comparisons across Trusts less meaningful but observations and trends within single Trusts should be fairly reliable.

The findings mirror the trend in HIV prevalence found in the HPA HIV Unlinked Anonymous Survey of Pregnant Women through Dried Blood Spot Surveys, showing stability since 2004 (29/10,000 cards tested positive in 2000, 40/10,000 in 2002 and 42/10,000 in 2006) [4, 10]. There are evident inequalities in the prevalence of HIV across London, consistent with findings from the confidential reports of HIV-positive pregnancies to the Royal College of Obstetricians and Gynecologists in the National Study of HIV in Pregnancy and Childhood; data for 2003-2004 indicated that prevalence of maternal HIV infection was the highest in North Central London (5.8/1,000) [11].

Data sources and availability

Not all London NHS Trusts appear to be able to provide all the required information. Implementation of simple and robust methods for monitoring uptake of screening in antenatal patients has been recommended [9]. There are still some limitations though, as the surveillance is not based on individual records, but on aggregated numbers. Denominators and numerators are often obtained from

TABLE

Prevalence of HIV, hepatitis B and syphilis infection and susceptibility to rubella per 1,000 pregnant women tested, by London Strategic Health Authority and National Health Service Trusts. Health Protection Agency Antenatal Infection Screening Surveillance, London, 2007)

Strategic Health Authority	National Health Service Trusts (i.e. public hospitals)	Prevalence per 1,000 tested			
		HIV	Hepatitis B	Syphilis	Rubella susceptibility
North Central London	Barnet & Chase Farm	1.9	7.9	3.2	47.9
	North Middlesex	10.1	20.9	16.3	55.4
	Royal Free	0.5	8.0	0.2	37.4
	University College	2.9	8.3	-	42.9
	Whittington	2.3	16.1	4.7	40.5
North East London	Barking, Havering and Redbridge	2.8	13.2	5.7	42.3
	Homerton	4.7	23.9	8.8	35.3
	Newham	6.3	14.9	6.7	56.3
	Royal London	0.8	13.4	5.4	64.7
	Whipps Cross	3.5	21.6	6.8	62.5
North West London	Central Middlesex	2.4	15.7	5.2	59.4
	Chelsea & Westminster	1.5	4.3	1.0	34.7
	Ealing	0.6	10.8	4.8	59.9
	Hillingdon	1.0	7.0	1.8	34.6
	Northwick Park	2.5	7.1	2.0	78.4
	Queen Charlotte's	0.6	5.9	1.6	17.4
	St. Mary's	2.6	9.3	6.4	31.5
	West Middlesex	2.6	5.8	2.0	31.2
South East London	Farnborough	0.2	2.6	1.2	23.0
	Guy's & St. Thomas'	6.7	17.5	5.9	45.8
	King's College	4.3	19.0	7.2	36.4
	Lewisham	7.9	16.1	5.9	59.6
	Queen Elizabeth	5.6	17.2	2.2	26.7
	Queen Mary's	2.2	4.8	0.9	41.2
South West London	Kingston	1.0	3.9	0.5	24.5
	Mayday	3.9	11.3	0.8	19.4
	St. George's	4.4	10.0	2.5	52.2
	Epsom & St. Helier	1.1	4.5	1.7	16.2

different sources (i.e. laboratory and maternity units and their various computer systems). Aggregated data cannot be cross-checked and do not allow us to explore co-infection or correlations in high rates of infections (e.g. in some Trusts, hepatitis B rates are very high but not correlated to high rates of HIV or syphilis infection). The HPA-coordinated AISS does not involve the private sector. However, almost all antenatal care in London is provided through the NHS [6].

The AISS is of particular public health interest for infections other than HIV, which are not monitored through alternative dedicated scheme. The estimated prevalence of syphilis (screen test positive) in pregnant women is around one in 200 but the increasing numbers of cases of syphilis among women in the UK [12,13] suggests that high rates of antenatal testing should be maintained to prevent future cases of congenital infection.

An assessment of vaccination coverage among babies at risk of vertical transmission of hepatitis B in 2006 showed that less than half of the babies born to HBsAg-positive mothers in London had received the four recommended hepatitis B vaccinations by the first year of age. There were important variations in performance across London [14]. This study enabled a limited validation of AISS data as it provided baseline information on the expected numbers of those at risk at each Trust in a particular timeframe. Aggregated data for pregnant women who decline antenatal tests recently have been added to the AISS questionnaire, to help better understand why uptake is not complete in all maternity units. A better understanding of the characteristics of individual infected women is needed as well. For this purpose a pilot of an individual based enhanced surveillance of HBsAg-positive mothers also began in London in 2008.

In the UK, as in many other European countries [15-21] there are different policies for universal antenatal infection screening. From a health-economics point of view, there is recent evidence in Europe that universal antenatal HIV screening is justified [22]. In the UK, cost benefit analysis has concluded that syphilis antenatal screening is worth continuing [23]. A recent study in France showed that surveillance of congenital syphilis cases, as well as assessment of syphilis screening practices during pregnancy, should be performed to prevent the occurrence of congenital syphilis cases [24]. An Italian study found prevalence of positive syphilis serology among 0.49% of pregnant women and authors concluded that antenatal syphilis screening is important, facilitates treatment during pregnancy and prevents vertical transmission [25]. Syphilis screening tests need to be followed by further diagnostic tests to confirm infection and assess its stage as well as any potential infectivity and risk to the unborn child.

We believe that the Antenatal Infection Screening Surveillance system described here is an effective method of monitoring policy implementation through provision of simple, relatively cheap and timely information. This provides the local health care providers with comparative data and indicators of their relative success. Maternity unit practices have been described as the most important predictor for determining uptake of HIV testing [26]. Local studies of possible reasons for not achieving universal testing are needed. This would help to ensure that practices are appropriately monitored at local level and results of this monitoring are used to improve antenatal screening, provision of treatment for infected mothers and interventions to prevent infection in the unborn child and among contacts of the mother.

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PREVALENCE OF HUMAN CYTOMEGALOVIRUS CONGENITAL INFECTION IN PORTUGUESE NEWBORNS

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Human cytomegalovirus (HCMV) is considered the most frequent cause of congenital infection, occurring in 0.2 to 2.2% of all live births. Since this is a wide range of prevalences observed in different studies, it would be desirable to investigate the prevalence of this infection at national level. The aim of this study was the evaluation of the national prevalence of HCMV congenital infection. We analysed a total of 3,600 Guthrie cards collected from Portuguese newborns during a period of 14 months (August 2003 to September 2004). The cards covered all regions of Portugal and were proportional to the number of births in each region. A heat DNA extraction method was used, followed by DNA amplification by nested PCR. Sensitivity and specificity of this method were evaluated as 93% and 100%, respectively, using 28 cards from HCMV-positive and 280 cards from HCMV-negative children. The national prevalence of congenital HCMV was determined as 1.05% (95% confidence interval: 0.748-1.446). This is the first study of the prevalence of HCMV congenital infection at national level in Portugal. It suggests that Portugal may have one of the highest prevalences of congenital HCMV infection in Europe.

Introduction

Human cytomegalovirus (HCMV) is considered the most frequent cause of congenital infection, occurring in 0.2 to 2.2% of all live births [1]. Since this is a wide range of prevalences observed in different studies, it would be desirable to study the prevalence of this infection at national level. To our knowledge, only one study about the prevalence of HCMV congenital infection in Portugal has been published. It used urine detection by the shell-vial method, and the estimated prevalence was 0.7% [2]. However, the above study was performed at only one hospital, making it difficult to extrapolate the results to the national prevalence. For an estimation of the national prevalence, urine samples from all the regions in the country would have to be collected, proportional to the number of births from each region, and HCMV would have to be detected by cell culture. However, this approach is not feasible to perform.

Dried blood spots (DBS), also known as Guthrie cards, have been used both for late detection of HCMV congenital infection (after the first three weeks of life) and for epidemiological studies with promising results [3,4]. Since all the DBS collected in Portugal for metabolic neonatal screening are sent to a national reference laboratory – the Jacinto de Magalhães Institute of Medical Genetics – and stored there for several years, the use of these cards

allow sampling from all Portuguese regions, which would be very difficult with viruria tests.

The aim of this work was the study of the prevalence of HCMV congenital infection in Portuguese newborns, based on the above collection of DBS. The methodology used was adapted from a technique previously described by an Italian team [5]. The first step of this study was therefore the determination of the sensitivity and specificity of this technique, when compared with the reference method, i.e. the detection of HCMV in urine by cell culture. The second step was the study of the national prevalence.

Material and methods

Sensitivity and specificity of nested PCR on DBS

Samples

Sensitivity was studied using Guthrie cards from 28 children with HCMV congenital infection as determined by detection of HCMV in the urine by shell-vial culture during the first three weeks of life. Specificity was studied using Guthrie cards from 280 neonates without HCMV infection (no detection of HCMV in the urine by shell-vial culture during the first three weeks of life). All cards were from children between one month and eight years of age at the time of our study. The DBS had been collected in the first week of their life and stored at the Jacinto de Magalhães Institute of Medical Genetics. For our study, this institute sent the cards, with the parents' consent, to the Hospital Centre Cova da Beira.

Molecular analysis

We used a heat-induced DNA extraction method, followed by amplification of HCMV DNA in a nested polymerase chain reaction (PCR), using a protocol adapted from Barbi et al. (2000) [5]. Each sample was tested in triplicate.

Blood was eluted from the Guthrie cards, and the DNA was extracted using a heat-induced protocol. A nested PCR protocol was used to amplify a region of the HCMV genome coding for the gp58 subunit of glycoprotein B [6]. The following oligonucleotide primers were used:

Outer primers:

- gB1: 5'-gAggACAACgAAATCCTgTTgggCA-3'
- gB2: 5'-gTCgACggTggAgATACT-gCTgAgg-3'

Inner primers:

- gB3: 5'ACCACCgCACTgAggAATgTCAG-3'
- gB4: 5'TCAATCATgCgTTTgAAgAggTA-3'

The sensitivity of this nested-PCR technique had previously been tested by us and shown to consistently detect HCMV in a suspension of 900 copies/ml of the laboratory strain AD-169 (unpublished data). Two different concentrations of AD-169 were processed as positive controls in each set of PCRs, and water was processed as negative control in quadruplicate. Disks punched from blank Guthrie cards were processed as additional negative controls and tested along with the samples. The cards that gave a positive result in at least one of the triplicate amplifications were retested with a new series of disks.

Viral culture

Viral cultures were grown at the Hospital Centre Cova da Beira or at the Hospital de Santa Cruz, using shell-vial assays in human foetal lung fibroblast cells (MRC-5 line), using a protocol previously described by Gleaves et al. (1985) [7], with minor modifications. The cells were analysed by immunofluorescence using anti-HCMV pool I.E.A.+E.A. monoclonal antibodies which give a typical nuclear signal in HCMV infected cells.

Prevalence of HCMV congenital infection in Portuguese newborns

We studied a total of 3,600 dried blood spots (DBS), that had been collected from Portuguese newborns during a period of 14 months (August 2003 to September 2004) and sent to the national screening laboratory. These newborns were from all regions of Portugal, including the Azores and Madeira. The number of Guthrie cards studied was proportional to the number of births in each region (data from the Jacinto Magalhães Institute of Medical Genetics). Within each region, the cards were randomly chosen and sent anonymously to the Hospital Centre Cova da Beira. The study was approved by the Comissão Nacional de Protecção de Dados (National Data Protection Commission).

DNA extraction and PCR were performed as described above.

Results

Sensitivity, specificity and negative and positive predictive values of the nested-PCR on DBS

Specificity

Of the 280 cards from uninfected individuals, 267 were negative in all three PCR tests. The remaining 13 cards were positive in one of the three PCR tests. On repetition, these 13 cards were negative in all three PCR tests (total: 1/6 positive tests). Therefore, no card among the 280 negative controls had more than one positive amplification out of six, and this was established as the cut-off for discrimination between positive and negative cards. The 13 single-positive PCR results were assumed to have been caused by a laboratory contamination during the amplification step, and were considered false-positive results.

Sensitivity

Of the 28 cards from HCMV-infected individuals, 26 had more than three positive amplifications in six PCR tests and were considered positive. Two cards were under the cut-off described above ($\leq 1/6$ positive amplifications) and were considered negative.

With these results, the sensitivity, specificity, negative and positive predictive values of this nested-PCR with the criteria described above were, respectively, 93%, 100%, 99% and 100%.

Prevalence of HCMV congenital infection in Portuguese newborns

The above method and cut-off were used to estimate the prevalence of HCMV congenital infection in Portugal. Of the 3,600 Guthrie cards tested, 38 were positive, according to the criteria

described above. This corresponds to a prevalence of 1.05% (95% confidence interval; exact binomial method: 0.748-1.446).

Discussion

The importance of studying the prevalence of congenital HCMV infection, the most frequent congenital infection [1], should not be underestimated. Updated evaluations of the impact of this infection are needed in order to raise awareness of the true burden of congenital HCMV infection and disease, allocate public health resources, and determine the cost-effectiveness or cost-benefit of potential interventions [8]. Determination of the congenital HCMV prevalence in each country would certainly benefit this purpose.

This is the first study on the prevalence of HCMV congenital infection at national level in Portugal. The 3,600 cards tested covered all regions of Portugal and were proportional to the number of births in each region, so that the samples represented all the Portuguese territory. To our knowledge, this is also the first study using Guthrie cards from all regions in one country to estimate a national prevalence, although one multicentric study used this technology for the determination of the prevalence of congenital HCMV in Italy [4].

The methodology used in the present study was adapted from a method described by an Italian team [5], which was reported to have 100% sensitivity and 99% specificity compared to the reference method, virus isolation in cell culture. Therefore, the first step of our study was to determine the sensitivity and the specificity of the adapted protocol used by us.

For the sensitivity analysis, we included DBS from all children diagnosed with CMV congenital infection between 1995 and 2001 who had been tested with the reference method at the Hospital Centre Cova da Beira and the Hospital de Santa Cruz and who fulfilled the inclusion criteria, i.e. signed informed consent from the parents and availability of a DBS collected in the first week of life before receiving any blood transfusion. A total of 28 cards were tested, obtained from symptomatic and asymptomatic infections, but also from children for whom clinical information was not available, which was the case for the two negative results. These two had had a positive urine culture result and we therefore consider them false-negatives.

Because the viral load was not determined in the above mentioned laboratories in 2004 and urine specimens were not preserved until 2007 (when they introduced routine determination of CMV viral load), the relationship between false-negative results, clinical information and low viral loads could not be ascertained in this study.

Interestingly, our recent experience with an external proficiency panel of samples (CMV DBS, organised by Quality Control for Molecular Diagnostics from the European Society of Clinical Virology) suggests that low viral loads could be the main factor responsible for false-negative results (unpublished data). Other possible explanations for the two false-negative results could be ineffective DNA extraction or the presence of inhibitory substances in the specimen; this was not checked in this evaluation because the technique described by Barbi et al. (2000) does not include an internal control [5]. Nevertheless, the 100% sensitivity obtained by the Italian team suggests that PCR inhibition is not a significant problem inherent to this technique.

Our results of 93% sensitivity and 100% specificity were encouraging and allowed us to proceed with the aim of this study, the determination of the prevalence of HCMV congenital infection in Portuguese newborns. The observed prevalence of 1.05% was within the expected range [1], albeit a little higher than in some of the latest European reports [4,9,10]. According to a recent meta-analysis of selected studies which had used the reference method and analysed at least 800 urine or saliva samples, the prevalence in European countries ranged from 0.3 to 0.5%, but only studies from Belgium, Denmark, Italy, Sweden, and the United Kingdom were included in this review [11].

One possible explanation for our results could be the high seroprevalence of around 80% in pregnant women in Portugal [12], because a positive correlation between maternal seroprevalence and birth prevalence has been described: one meta-analysis suggested maternal seroprevalence as a significant predictor of birth prevalence, with every 10% increase in maternal seroprevalence corresponding to a 0.26% increase in birth prevalence [8]. However, this cannot be the only explanation, since Barbi et al. (2006) also described a seroprevalence of 80% in women of childbearing age, whereas it identified only 0.18% of newborns with congenital infection in. Interestingly, the same team reported 0.47% congenital infection in a previous study [13]. Whether this discrepancy was the result of different methodologies or sample size (9,032 pooled DBS in the study from 2006 versus 1,268 urine cultures in 1998) or due to other factors, is unclear.

In the present study, a higher sampling could have narrowed the confidence interval, but for practical reasons, the sample size had to be limited to 3,600 cards. Since the methodology implied that each card must be tested in triplicate, followed by a further three amplifications for those with a positive result, more than 10,000 individual nested-PCR reactions had to be performed in the current setup of the study.

Considering that the sensitivity of the method was 93%, the maximum proportion of expected false-negative results would not have had a significant influence on the final prevalence (1.05% could have been 1.14%). On the other hand, the specificity in the first phase of the study was 100%, assuring a very low probability of false-positive tests in the second phase. However, specificity was studied in only 280 cards and it cannot be ruled out that a false-positive result may have occurred if more cards had been analysed.

Since the cards for prevalence determination were sent anonymously, we could not obtain clinical information, including maternal serological evolution during pregnancy. Another study coordinated by the Portuguese Society of Paediatrics, currently addresses this point in order to figure out the relative importance of maternal primary and recurrent infections in the Portuguese children with congenital CMV infection.

With around 105,000 births per year, a prevalence of 1.05% translates to about 1,103 children (between 785 and 1,518, with a 95% confidence interval of 0.748-1.446) born in Portugal each year with this congenital infection. Assuming that around 11% of these infections will be symptomatic at birth [8], about 121 (between 86 and 167) of the infected newborns will have signs and/or symptoms, and at least half of them will present late sequelae. To these numbers must be added an estimated 13.5%, i.e. about 149 (between 106 and 205) children with asymptomatic infection at birth, who will suffer from late sequelae, particularly sensorineural hearing loss and cognitive impairment [11].

In conclusion, for the first time in Portugal a nationwide study using DBS allows us to estimate the number of children congenitally infected with CMV. Our data suggest that Portugal may have one of the highest prevalences of congenital CMV infection in Europe, although nationwide studies in other European countries are needed before any conclusions can be drawn.

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PREVENTION OF CONGENITAL RUBELLA AND CONGENITAL VARICELLA IN EUROPE

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Rubella and varicella zoster virus (VZV) infections during pregnancy can cause severe adverse outcomes in the embryo or foetus. Despite the availability of safe and efficacious vaccines, cases of congenital rubella and varicella syndrome still occur in Europe. As of 2004, several countries had high proportions of women of childbearing age that were susceptible to rubella and varicella virus infection. Effective immunisation strategies to enhance prevention should include an active role of different medical specialists in order to include all medical consultations a person may have at different points in their lives as an opportunity to immunise susceptibles. Linkage of data on infectious diseases with those from congenital defects registries may be helpful to monitor the epidemiology of congenital rubella and varicella.

Introduction

Women have an increased risk of acquiring certain transmissible diseases during pregnancy due to transient immunosuppression [1]. Although many infectious diseases can be prevented by vaccination during childhood, appropriate immunisation of women of childbearing age is crucial in preventing diseases in their offspring that may occur during embryonal/foetal life or early after birth. Because many immunisations, if performed during pregnancy, may theoretically pose a risk for the unborn child, immunisation strategies should be integrated where possible with preconceptional care.

Prevention of congenital rubella syndrome is one of the priorities set by the World Health Organization (WHO) Regional Office for Europe. In 1998, the target of one case of CRS per 100,000 live births by 2010 was approved as a goal of immunisation programmes in the Region [2,3].

This paper tries to draw a picture of the epidemiology of rubella and varicella infections in Europe and the potential for their transmission to pregnant women and presents with possible strategies to enhance prevention of these infections.

Rubella Epidemiology

Reliable data on the incidence of CRS are difficult to obtain for various reasons: because of weakness of the surveillance systems, because rubella in pregnancy can be asymptomatic, because CRS can present with incomplete clinical signs, and because specific symptoms may appear late in the infection.

From 2001 to 2003, a total of 47 cases of CRS were reported from member states of the WHO European Region, decreasing from 21 cases in 2001 to 12 cases in 2003 [4-6]. Moreover, 36% of these cases were reported from Romania and 32% from the Russian Federation, whereas the last CRS cases in Finland and Denmark, where coverage for MMR vaccine has been high for many years, was recorded in 1986 [7]. In 2004, 15 member states did not report information on CRS to the WHO, but 14 member states reported 17 cases of CRS [2]. In Italy, where a national campaign for measles and CRS elimination has been reinforced since 2003 [8], the annual incidence rate of CRS has consistently exceeded the WHO goal of one per 100,000 newborns between 1996 and 2002, with a peak in 2001 of six per 100,000 [9,10]. Recent data suggest that rubella outbreaks still occur in women of childbearing age in Italy. In the period between 2005 and 2008, 30 confirmed cases of rubella have been reported in pregnant women, and four confirmed CRS cases have been diagnosed [11].

The trend of rubella infections in European countries can be obtained from data reported to the WHO by the countries of the WHO European Region, and from data reported to EUVAC.NET, a European surveillance network for vaccine preventable diseases that includes 18 European Union countries [12]. Data reported to the two systems from 2000 to 2007 are shown in figure 1 [12]. Data from both surveillance systems indicate a sharp decrease in the number of cases after 2003, and a stable number of cases since 2005.

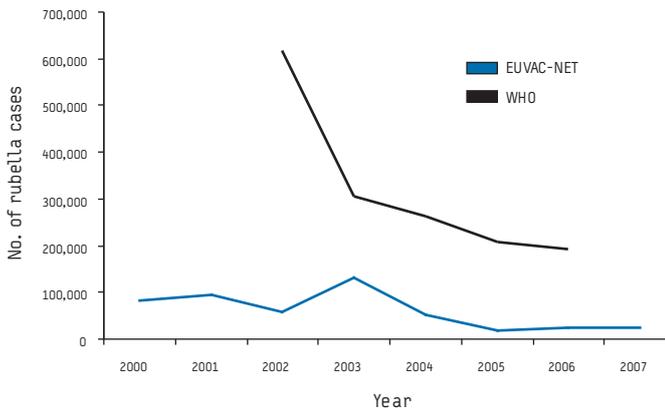
According to the European Centre for Disease Prevention and Control (ECDC), 1,498 rubella cases were reported from 22 countries in 2005. The highest incidences were reported by Lithuania (3.44 per 100,000) and the Netherlands (2.23 per 100,000). The overall incidence in the 22 countries was 0.51 per 100,000 [13]. As a result of suboptimal immunisation coverage for rubella, several outbreaks have been recorded in Europe in the last decade. In the period from 2002 to 2003, a large rubella outbreak was observed in Romania with 115,000 reported cases mainly in school-aged children with no difference in incidence by sex [14]. A large rubella and CRS outbreak was described in 1993 in Greece, with 25 serologically confirmed cases (24.6 per 100,000 live births); the incidence decreased after this, but another epidemic occurred in 1999, mainly in young adults, with four cases of CRS (4.0 cases per 100,000 live births). The CRS incidence in Greece remained low until 2003 [15,16]. Rates of CRS as high as 350

per 100,000 live births have been described during outbreaks in the Russian Federation between 2002 and 2004 [1]. In Turkey, there was no surveillance system for rubella and CRS until 2005. In 2005, with a new surveillance system, 2,245 rubella cases were reported – an incidence rate of 3.1 per 100,000 inhabitants – and only one case of CRS in the same year [17]. In the United Kingdom (UK), measles-mumps-rubella (MMR) vaccination controlled rubella in children and women of childbearing age, but an epidemic in 2005 showed that individuals born between 1982 and 1986 who had never been previously exposed to natural infection were still susceptible [18-21].

Seroprevalence data from the European Sero-Epidemiology Network (ESEN) study performed between 1996 and 2003 showed that women in several countries included in the study were not sufficiently protected against rubella infection (Figure 2) [22].

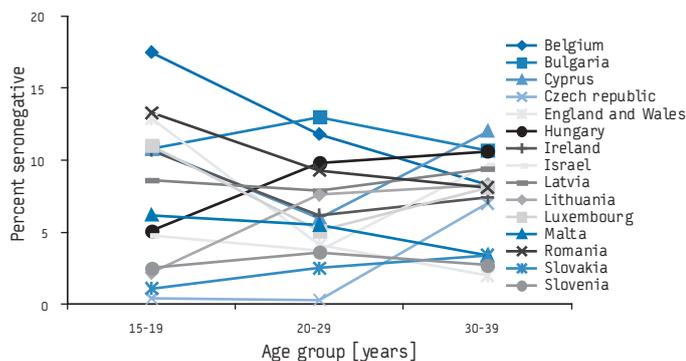
In Finland and the Netherlands on the other hand, a low rate (<5%) of susceptibles in childhood and adolescents of both sexes was observed in the period from 1996 to 2004 [7,23]. In Italy,

FIGURE 1
Reported number of rubella cases to WHO and EUVAC.NET, 2000 - 2007 (n=2,073,229)*



* source: [11,23,24]

FIGURE 2
Proportion of women susceptible to rubella, by age group, 1996 - 2003*



* source: [16]

seroprevalence data from 2004 showed 11% of susceptible women in the age group of 15-19 year-olds, and 8% in the 20-39 year-olds [11].

Prevention strategies

In order to meet the WHO target of one case of CRS per 100,000 live births by 2010 and to achieve elimination of measles, a measles and CRS elimination strategy was launched in 2002 [3]. The success of current policies in countries using the rubella vaccine has been considerable. The use of rubella combined vaccine has markedly increased since 2002 in the European Region. However, eastern European countries have only recently introduced the MMR vaccine, and some countries in western Europe, where the vaccine has been used for a longer time, have historically had inadequate coverage rates (Table) [18]. In addition, several countries have only recently moved from a one-dose strategy to a two-dose strategy for rubella-containing vaccine [3,12,24].

Use of rubella-containing vaccine in WHO/Europe member states has increased from 38 (75%) of 51 countries in 2001 to 48 (92%) of 52 countries in 2007; Currently 47 member states use at least one dose of a combined MMR vaccine in their childhood immunisation programmes [3,24]. Given that most countries in Europe have chosen to use combined measles-rubella (MR) or MMR vaccines, rubella elimination is feasible within a framework of measles elimination [12].

Rubella-susceptible women immigrating from outside Europe have been identified as an important target group for immunisation. Programmes to immunise newly arrived women and adolescent girls are necessary, because they may have contracted rubella in a high-incidence country that does not have a rubella immunisation programme and give birth to an infant with CRS. International vaccination centres should make an effort to immunise immigrant people visiting friends and relatives outside Europe. Several supplementary immunisation activities targeting measles- and/or rubella-susceptible individuals have been conducted in several countries since 2001, including Albania, Cyprus, Italy, Kazakhstan, Kyrgyzstan, Moldova, Montenegro, Serbia, Tajikistan and Turkey [24].

Overall, about 70% of member states had national immunisation plans in 2004, 60% had measles elimination plans, but less than 50% had rubella elimination plans and/or plans for CRS prevention [24].

Varicella Epidemiology

The epidemiology of congenital varicella (CV) can be derived only indirectly from ad hoc studies because no European country has a specific surveillance system in place. Moreover, in some European countries Denmark, Iceland, Ireland, Northern Ireland, Norway, Sweden, Switzerland and Turkey, varicella disease is not under surveillance. Others Belgium, England and Wales, France, Germany, the Netherlands and Portugal have data derived from sentinel surveillance systems [25,26].

More than 90% of European children contract chickenpox in the first 10-12 years of life [27-30]. In 2002-2003 the estimated incidence in the UK was 262 varicella cases per 100,000 nulliparous women aged 15-44 years, with 10 of these cases occurring during pregnancy and resulting in nearly 0.06 cases of congenital varicella and 0.16 cases of neonatal varicella per

100,000 live births [25,28]. In 2002-2003, the majority of varicella cases in European countries were reported from Spain (28%), Poland (18%) and Italy (14%) [26,31].

In Italy, only 78% of 15 year-olds had antibodies to VZV between 1996 and 2003, and 18% of female teenagers were seronegative for VZV [25,30,31]. In the same period, nearly 90% of people in the UK had serological evidence of infection by the age of 20 years [28,30]. In Spain, the prevalence of VZV antibodies in the period from 1996 to 2003 was 94% in pregnant women aged 15-24 years, 95% in those aged 25-29 years and >95% in those aged 30-49 years [30-32]. The seroprevalence was 97.8% at the age of 10 years in Switzerland, and more than 90% at the age of nine years in Belgium, in the season 2000-1 [26,31].

In most European countries less than 5% of women of childbearing age (between 15 and 39 years-old) were seronegative for VZV in the period from 1996 to 2003, except in Italy (12.6%), Israel (7.6%), and Ireland (5.4%). In Finland, VZV seroprevalence was 96.2% in 2000 [31-33].

Prevention strategies

Safe and effective vaccines against varicella have been available in Europe for the last ten years. The increase in the age at onset, the burden of complications and the direct and indirect costs have prompted several countries to consider universal immunisation programmes for varicella.

Germany is the only country in Europe that has a routine universal childhood varicella immunisation programme, introduced in 2004, with a single dose administered to children at the age of 11-14 months and a catch-up dose for adolescents aged 9-17 years who have a negative history of chickenpox [34]. In April 2006, the combined MMR-varicella (MMR-V) vaccine was licensed in Europe, but it is as yet not available. However, a two-dose MMR-V

schedule is likely to replace the monovalent vaccine at least in Germany [25,34].

In Spain, varicella vaccine is recommended for all healthy susceptible adolescents (≤ 13 years), all children with chronic diseases, organ transplant recipients, seronegative households and health contacts of high-risk children [25]. The community of Madrid adopted universal infant vaccination in October 2006 [25]. Other countries including Cyprus, Italy, Latvia, Slovenia, Switzerland, and the UK recommend immunisation to high risk patients, seronegative healthcare workers, seronegative family members of high-risk patients, and adolescents with no recollection of having had the disease [25].

No specific programmes or initiatives have been endorsed so far by the WHO to promote varicella immunisation or prevention of congenital varicella.

How to enhance prevention strategies

Integration of preconception components into primary care can better serve women at various levels of risk across their lifespan [35]. Depending on the age group in which prevention strategies should be applied, prevention of CRS and CV require a strong integration of several activities which involve different professional levels.

Children and adolescents

Universal immunisation programmes targeted to children are already in place for rubella. The WHO Regional Office for Europe developed and implemented a strategic plan for the prevention of measles and congenital rubella infection in the WHO European Region in 2002 [3]. This plan targeted the elimination of measles and the prevention of congenital rubella infection for the year 2010.

TABLE

Vaccination policies for rubella in 16 countries as of 2003*

Country	Year of introduction of childhood rubella vaccination		Recommended age for second dose	Average vaccine coverage among infants (%)	Adolescent female vaccination (years)	Antenatal screening as of 2003	Average rubella incidence (per 100,000)
	One dose	Two dose					
Belgium	1985	1994	11	82 (1999)	1973-1994	Yes	0.2 (2001-2003)
Bulgaria	1992	2001	12	93 (1999-2003)	1988-2001	-	86.8 (1999-2003)
Cyprus	-	1989	4-6	86 (1999-2003)	1974-1989	Yes	0.2 (1999-2003)
Czech Republic	-	1986	2	97 (1999,2001,2003)	1982-1997	-	11.3 (1999-2003)
England and Wales	1988	1996	4-5	85 (1999-2003)	1970-1988	Yes	0.1 (1999-2003)
Hungary	1991	1999	11	100 (1999,2002,2003)	-	-	0.7 (1999-2003)
Ireland	1988	1992	4-5	76 (1999-2003)	1971-1988	Yes	1.6 (1999-2003)
Israel	1988	1995	6-7	95 (1999-2003)	1973-1999	-	0.2 (1999-2003)
Latvia	1993	2002	7	97 (1999-2003)	1993-2002	-	29.0 (1999-2003)
Lithuania	-	1992	6-7	97 (1999-2003)	1992-1996	-	20.2 (1999-2003)
Luxembourg	1986	1994	5-6	-	-	Yes	0.8 (2000-2001)
Malta	1989	1992	12	74 (1999-2003)	1976-1992	-	1.0 (1999-2003)
Romania	-	-	-	-	-	-	136.3 (1999-2003)
Slovakia	1985	1992	11	99 (1999-2003)	1985-1992	-	0.3 (1999-2003)
Slovenia	-	1990	6-7	93 (1999-2003)	1973-1990	-	0.5 (1999-2003)
Sweden	-	1982	12	92 (1999-2002)	1972-1982	-	< 0.1 (1999-2003)

* source: [17]

Nonetheless, the success in eliminating a transmissible disease depends mostly on the coverage level that is achieved. Measles elimination has already been achieved in some member states through routine immunisation programmes, which maintain high measles vaccine coverage using a two-dose schedule [2,36]. Since most European countries use combined measles vaccines including the rubella component, policies toward measles elimination should result in concurrent elimination of CRS [36]. Strategies for elimination of measles and CRS should be sustained in the entire WHO European Region maintaining coverage levels over 95% for rubella-containing vaccines. Catch-up programmes must also be maintained to avoid the accumulation of susceptibles in the general population. It should be considered that it is unlikely that universal programmes for varicella immunisation will be implemented in the short term in all countries of the WHO European Region. The recent licensure of MMR-V, however, may favour a link with measles and congenital rubella elimination strategy in the near future. Since patients reliably remember having had varicella, a minimal approach for prevention of varicella in pregnancy may consist of a verbal screening of adolescents to choose those eligible for immunisation. Some countries already actively offer varicella immunisation to high risk children. Although this strategy is directed to a small proportion of the general population, it is essential to monitor its impact. If susceptible individuals accumulate as an effect of targeted immunisation strategy, outbreaks may occur in this group at an older age, when varicella is more likely to be severe [37].

These potential strategies rely on the integration of roles of public health officers with those of family paediatricians and general practitioners [27].

Women of childbearing age

Information programmes should be in place to disseminate and to promote screening and immunisation against measles, mumps, rubella, and varicella in susceptible women of childbearing age. These programmes may be particularly effective if not limited to women who plan a pregnancy. Every visit of this target population to a gynaecologist or general practitioner may include counselling, screening, and oriented recommendations for immunisation. It is necessary to include rubella virus antibody screening in prenatal care even in countries with well-established vaccination programmes. One needs to keep in mind that people do not reliably recall a past rubella infection and that, in cases where it is not possible to determine the immunisation status or the presence of specific IgG antibodies, a woman must be considered susceptible. Vaccines against rubella and varicella infections should be offered to all women of childbearing age who do not have acceptable evidence of immunity [38,39].

Women during pregnancy

Screening and diagnosis of rubella and varicella infections during pregnancy pose particular problems. Communication of screening results to pregnant women may result in termination of pregnancy [38,39]. Besides the fact that the performance of commercial diagnostic tests is variable, it must be kept in mind that as the true incidence of a certain disease becomes low, the positive predictive value of diagnostic tests for confirming recent infection declines as well. This is particularly relevant for rubella infection in countries in which elimination has almost been achieved [22,39]. A woman identified as susceptible to rubella or varicella should be followed until the end of pregnancy to ensure that she will be immunised soon after delivery [22,39].

Women after delivery or abortion

Since delivery or abortion take place in medical facilities, this setting is particularly appropriate for administering due immunisations provided that information on previous screening is communicated. Cost-effectiveness analysis of antenatal varicella screening with post-partum vaccination of susceptibles suggests that the screening and vaccination strategies are more cost-effective in preventing cases in women than with the strategy to treat cases as they arise [27]. In case information on screening is not available, diagnostic tests may be offered to women with unknown susceptibility to rubella and varicella [27,39].

Women who have already had children are very likely to consult a family paediatrician before another pregnancy. For this reason, mothers can be verbally screened and provided with specific recommendations during paediatric consultation. This strategy could be added to that based on visits to general practitioners.

Surveillance and seroprevalence

The WHO Regional Office for Europe launched a strategic plan in 2005 to eliminate congenital rubella [3]. A European measles and rubella laboratory network was established in 2002 [3]. At present, 47 member states (90%) have a national measles/rubella laboratory, which is linked to one of three WHO European Region reference laboratories appointed in 2003 or to the specialised laboratory located in the European Region. The network has implemented standardised diagnostic methods and reagents, and a quality assessment programme, including proficiency testing and monthly online reporting of laboratory performance indicators; completeness of reporting from national laboratories was 70% in 2004 [3]. Seroprevalence studies should be encouraged periodically to precisely identify population groups that may be targeted for special prevention strategies. While surveillance of rubella is in place in all WHO European countries and many of them also have a system for varicella, much effort should still be devoted to surveillance of congenital rubella and congenital varicella [4,25]. Moreover, member states use different methods to collect measles and rubella data, including aggregate, case-based, and sentinel physician reporting, which require standardisation [2]. This activity could benefit from cooperation between public health professionals working in surveillance of transmissible infections and congenital defects registries regarding the sharing of data and the use of similar case definitions. Under-notification is a well recognised limitation of nationwide mandatory notification systems. It is therefore necessary to enhance the quality of surveillance systems and sero-epidemiology, particularly in countries in which the disease is under control [1,20,25].

Integration with other prevention strategies

Women of childbearing age should receive preconceptional counselling whenever they interact with medical facilities. General and hospital practitioners, gynaecologists and obstetricians, and possibly professionals in other specialties, should offer information for the prevention of adverse events in pregnancy advocating appropriate lifestyle habits, food and vitamin intake, and prudent use of drugs. Prevention of transmissible disease through immunisation, not only against rubella and varicella, should be one of the most important parts of preconceptional counselling.

Conclusions

Preconceptional screening and immunisation of pregnant women are not yet adequate in Europe. European countries should endorse common strategies to improve as much as possible the impact of recommendations for the prevention of rubella and varicella

in pregnancy. This is possible only through the coordination and integration of several activities and different actors who should share the final goal of preventing cases of these diseases.

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Research articles

FACTORS AFFECTING THE ADHERENCE TO AN ANTENATAL SCREENING PROGRAMME: AN EXPERIENCE WITH TOXOPLASMOSIS SCREENING IN FRANCE

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Monthly serological testing is mandatory in France for pregnant women not immune to toxoplasmosis. We assessed for the first time the adherence to this national programme, using data from antenatal tests for *Toxoplasma* antibodies collected by the Union of Health Insurance Services in the French Rhone-Alpes region. Data from 34,290 pregnancies was analysed. The first test was done late in 25% of women (8,430). Women had on average 5.7 tests during pregnancy, only 40 percent (13,774) were tested seven or more times as recommended. Young women were more likely to have a late first test, but age did not significantly influence regularity and number of tests. Free medical coverage favoured a late first test, fewer tests and longer between-test intervals. An early first test did not affect test numbers or between-test intervals. A re-useable prescription for several tests was associated with better adherence. Prescription by general practitioners was associated with an earlier first test, but fewer tests and longer between-test intervals. When prescribing physician(s) included a gynaecologist, the first test was more likely to be behind schedule, but the overall number of tests was higher and between-test intervals shorter. Because data was collected through private laboratories, our conclusions apply to the majority of French patients who need to schedule a separate visit for blood testing after prescription.

Introduction

Congenital *Toxoplasma* infection arises in 25% of acute maternal infections during pregnancy. The consequences for the foetus can be severe, most often ophthalmologic or affecting neurodevelopment [1,2], and are diagnosed immediately, at birth or later during childhood or adulthood [2]. In an attempt to decrease the number of children with severe infections, several countries have implemented mandatory or recommended antenatal testing programmes in order to promptly recognise and treat acute maternal *Toxoplasma* infections. In France, an antenatal screening programme was implemented in 1978. It has included, since 1985, detection of antibodies against *Toxoplasma* before the end

of the 12th week of gestation - the official deadline for registering a pregnancy - followed, since 1992, by a monthly testing until the time of delivery for patients who are not immune. There is a recommended minimum of seven tests. The preventive impact of this programme remains to be proven. Adherence to this programme is also relevant when debating its effectiveness, but has never been addressed. We present here an analysis of the adherence to the French screening programme for congenital toxoplasmosis. It is specifically targeted to women who are tested in private laboratories, which is common for outpatients in France. This feature of the French health care system requires an obligation on the patients' part to schedule the different appointments for blood sampling. Patients need to pay for the tests, but will be reimbursed, provided that the tests were prescribed by a physician (general practitioner (GP) or any specialist doctor) or a registered midwife.

The goals of our study were to assess adherence to the programme and to identify reasons for poor adherence, in order to develop a communication strategy specifically targeted to pregnant women and their physicians.

Patients and methods

Available data

We used data collected for reimbursement purposes by the Regional Union of Health Insurance Services (URCAM) of the French Rhone-Alpes region. They record the biological analyses performed at private laboratories and reimbursed for the part of the population (86%) insured by the main health insurance system. The national coding system for biological analyses allows differentiation between the first antenatal test, intended to determine the patient's immunity, and subsequent follow-up tests required to exclude later seroconversion. For each test, dates of issue of prescription and date of blood sampling were available, along with information on the professional who prescribed the test (GP, obstetrician-gynaecologist, other specialist or registered midwife, public or private practice). Patient data included age at delivery, dates of conception and

delivery, whether she delivered in a private or public hospital, and whether she was fully covered by the national health service - free medical coverage (FMC) being attributed to low income.

Study population

We selected all women living in the Rhone-Alpes Region who delivered between 1 July 2002 and 30 June 2003 and for whom at least two tests for *Toxoplasma* infection were reimbursed, including one follow-up test. The aim was to select women who were not immune to toxoplasmosis and who were supposed to undergo the mandatory monthly testing schedule. Data was extracted anonymously by the URCAM statistics department and analysed by the biostatistics department of the Lyon teaching hospital.

Criteria

The first studied criterion was whether or not the first test had been performed within the first 12 weeks of pregnancy. Factors included in the analysis were: age, FMC, delivery in a public or private hospital, profile and type of practice of prescribing physician.

Two additional follow-up criteria were the mean number of tests throughout pregnancy and the mean time interval (in days) between two consecutive tests.

Statistical methods

Continuous variables were described with mean, median, standard deviation (SD), minimum and maximum. The mean between-test interval for each patient was calculated as the mean of the intervals between two consecutive tests uncorrected for potential correlation between intervals. Binary variables were described with number and percentage. Association between outcome and independent predictors was studied through different types of regression models: Logistic regression was used for the binary dependant variable "late first test". All variables linked to the women (age, FMC, delivery in a public or private hospital) as well as the profile of the prescribing physician(s) during pregnancy

were divided into four categories - GP(s) only, obstetrician-gynaecologist(s) only, GP(s) plus obstetrician-gynaecologist(s), other specialists (including registered midwives) - and entered into the model.

For the other two criteria, three further predictors linked to the first test were added to the previous set of variables: "tests done on schedule (yes/no)", "time interval between prescription and testing" and "prescription for the initial test re-used on at least one follow-up test (yes/no)". Poisson regression was used for the ordinal variable "number of tests", with the number of weeks of pregnancy as offset. All independent covariates tested individually reached statistical significance ($p < 0.01$), except the items related to the patients' first test, which were nevertheless considered as important and retained in the final model.

A linear regression model was run for the continuous variable "time interval between two consecutive tests". All variables were individually associated with a p value under 0.01 and kept in the final model, except for the re-use of prescription. Nevertheless, this factor was considered to be important and retained in the model. The effect of age was modelled as a linear relation after verifying several multivariable fractional polynomials models.

Statistical significance was accepted for $p < 0.05$. Analyses were performed using STATA® release 9 (Stata Corporation 2005, College Station, Texas, United States).

Results

Study population

There were 41,086 deliveries during the study period. For 38,450 women, two *Toxoplasma* antibody tests, including at least one follow-up test, were reimbursed. After exclusion of 4,160 women, 34,290 remained in the final sample. The reasons for exclusion and their number are given in the Figure.

The characteristics of patients, prescribing physicians and tests are presented in Table 1.

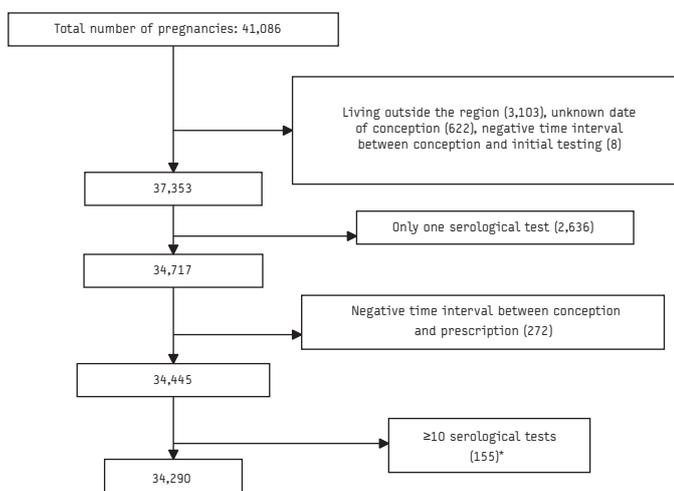
The mean age of the women was 29.5 years; 1,086 women (3.17%) were under 20 years-old and 467 (1.36%) over 40 years-old. Mean gestation was 37.6 weeks (SD 1.9). Most pregnancies lasted 37 weeks or more (24,882; 72.6%), very few lasted less than 34 weeks (1,164; 3.39%). A large proportion of women had one (15,068; 43.9%) or two (14,946; 43.6%) prescribing physician(s). The majority of women had all tests done in one (26,588; 77.4%) or two laboratories (6,599; 19.3%). Prescriptions for the first test were re-used for at least one more test by 2,832 (8.26%) patients. For 512 women (1.49%) there was a single prescription for the totality of the tests. The re-usable prescriptions were written by a GP for 707 (25.0%) of the 2,832 women, by an obstetrician-gynaecologist for 2,083 (73.6%), and by another specialist or a registered midwife for 37 (1.31%). Since almost all prescribing physicians (99.29%) were in private practices, this co-variable was disregarded in the following analyses.

Initial test

The first test was prescribed on average at 8.3 weeks of gestation (median 7.1; SD 5.0; min 0, max 36.6), in 60% of cases by a gynaecologist (Table 1). The mean time interval between prescription and testing was 7.9 days (median 3; SD 12.3, min 0, max 178); it was longer in younger women ($p < 0.0001$), in women with FMC ($p < 0.0001$), and when the test was prescribed by an obstetrician-gynaecologist rather than by a GP ($p < 0.0001$).

FIGURE

Exclusions from the data file with justification, antenatal toxoplasmosis screening programme, France, 2002/03



*Women who had more than ten tests reimbursed were excluded because this could suggest occurrence of a seroconversion.

The first test was performed at 9.5 weeks of gestation on average (median 8.4; SD 5.4, min 0, max 37.6). It was performed within the recommended schedule (in the first 12 weeks of pregnancy) in 75.4% of cases (25,860).

TABLE 1

Characteristics of women, prescribing physicians and tests, antenatal toxoplasmosis screening programme, France, 2002/03

Characteristics	Mean (SD; min-max)
Age of pregnant women	29.5 (4.9; 14-54)
Length of pregnancy (weeks)	37.6 (1.9; 21-44)
Number of prescribing physicians per patient	1.7 (0.74; 1-7)
Number of prescriptions per pregnancy	4.9 (2.0; 1-9)
Number of tests per pregnancy	5.7 (1.9; 2- 9)
Number of different laboratories used per pregnancy	1.3 (0.5; 1-6)
Number of weeks between first and last test	22.9 (7.7; 0-38)
	Number (%)
Free medical coverage	3,319 (9.7)
Delivery in a public hospital	23,537 (67.6)
Profile of physician who prescribed the first test	
General practitioner	13,431 (39.2)
Gynaecologist	20,569 (60.0)
Other	290 (0.8)
Profile of physician(s) who prescribed the follow-up tests	
General practitioner(s) only	6,596 (19.2)
Gynaecologist(s) only	15,864 (46.3)
General practitioner(s) and gynaecologist(s)	10,534 (30.7)
Other specialist(s)	1,296 (3.8)

SD: Standard deviation.

TABLE 2

Effects of the characteristics of women, physicians and the first toxoplasmosis test on the number of tests and mean between-test interval, antenatal screening programme, France, 2002/03

	Reference	Overall number of tests Risk ratio for one additional test [95% CI]	Mean between-test interval (days) Interval [95% CI]
Patient profile			
Age of pregnant women	Per year older	NS*	NS*
FMC	No FMC	0.84 [0.83;0.86]	6.02 [5.4;6.7]
Delivery in private hospital	In public hospital	1.04 [1.03;1.05]	-0.45 [-0.87;-0.03]
Testing profile			
First test late	Not late	0.70 [0.69;0.71]	-0.73 [-1.2;-0.2]
Interval between first test prescription and testing	Per 10 additional days	0.995 [0.994;0.995]	NS*
First prescription re-used for at least one test	Prescription not re-used	1.07 [1.29;1.47]	-4.7 [-5.4;-4.0]
Profile of prescribing physician(s)			
Gynaecologists(s) only	GP(s) only	1.08 [1.40;1.57]	-4.2 [-4.7;-3.6]
GP(s) + gynaecologist(s)	GP(s) only	1.16 [1.15;1.18]	-3.4 [-3.9;-2.8]
Other	GP(s) only	1.19 [1.16;1.22]	-4.3 [-5.4;-3.2]

*CI: confidence interval; FMC: free medical coverage; GP: general practitioner; NS: not significant.

Independent predictors for a delayed first test were: FMC (odds ratio (OR) 2.39; 95% confidence interval (CI) [2.22-2.58]), age (OR 1.03 95% CI [1.02-1.04] per year younger) and prescription by a obstetrician-gynaecologist (OR 1.29 95% CI [1.22-1.36]) or another specialist (OR 1.68 95% CI [1.30-2.18]) rather than a GP.

Test number and frequency

Number of tests

Women were tested on average 5.7 times (median 6; SD 1.9, min 2, max 9), an average adherence rate of 81% (see Table 1). 40.2 percent (13,774 women) were tested seven or more times, as recommended.

Independent predictors for a lower number of tests are summarised in Table 2: FMC (p<0.0001) had the greatest impact (incidence-rate ratio (IRR)=0.84; 95% CI [0.83-0.85]), followed by delivery in a public hospital (p<0.0001), GP(s) only as prescribing physician(s) (p<0.0001), a first test performed late (p<0.0001), a long time after prescription (p<0.0001), and a test done with a prescription that was not re-used (p<0.001).

Between-test intervals

The mean between-test interval was 37.6 days (median 32.7; SD17.9; min 0, max 229). Eighty percent (27,402) of women had at least one between-test interval exceeding 35 days, 22,954 women (66.9%) had two or fewer intervals exceeding 35 days. The intervals were significantly longer in women who had FMC (p<0.0001), delivered in a public hospital (p<0.0001), had only GPs as prescribing physicians, had a late first test (p<0.0001) or used multiple prescriptions (one per test) rather than a re-usable prescription (p<0.001) (Table 2).

Discussion

The goals of our study were to determine compliance with the screening programme for toxoplasmosis in pregnant women tested in private laboratories and to identify predictors for non-compliance. Compliance was unsatisfactory, with a quarter of the participants doing the first test too late, 80% of participants having at least one

between-test interval exceeding 35 days and 60% of participants completing fewer than the recommended seven tests.

These findings were based on a large dataset collected from the Rhone Alpes population which represented 9.7% of the total French population and 9.3 % of all births in 2003 [3]. It did not include women covered by the health care systems for agricultural or independent workers (14% of the population), but we have no reason to assume that the testing behaviour should be different in that subset of the population. Women who were not tested at all were also disregarded in the study, but these patients, whose number are impossible to estimate, are likely to have such a different profile that they would require a specific study to understand the reasons why they are not included in standard care. We can not rule out the possibility of a small proportion of women having a test and forgetting to apply for reimbursement, but considering the large amount of data in our file, it is unlikely that they significantly modified our conclusions. The number of pregnancies in our study was indeed consistent with the 76,349 births registered for 2003 in the Rhone Alpes region [3] and the estimated regional seroprevalence for *Toxoplasma* infection of 36.1% [4]. Furthermore, our data was in line with national estimates concerning mean age of pregnant women, rates of free medical coverage and of deliveries in a public hospital [5].

As no other study has been conducted since the French screening programme was implemented, it is unknown whether adherence has always been insufficient. Prenatal programmes for toxoplasmosis only exist in several other countries [6], although there are differences in the testing schedule and in how the sampling is organised. Data on compliance, however, have only been reported in one Brazilian study, which also found adherence to screening to be insufficient [7].

Compliance affects cost and effectiveness of screening [8], but the consequences of the substandard compliance observed in our study are difficult to measure. The earlier a patient at risk (i.e. a pregnant woman who has no immunity against toxoplasmosis) is identified, the more do they benefit from information on how to avoid infection. Consequently, late testing should be associated with a higher incidence of maternal infections. However, this cannot be measured in the absence of a notification system. There is also uncertainty regarding the effectiveness of health education [9]. Having a late first test that is positive for anti-*Toxoplasma* IgG makes it more difficult for the biologist to determine whether the infection was acquired before or after the beginning of pregnancy. This uncertainty generates additional costs for complementary testing as well as anxiety for the future parents.

In the event of seroconversion, long intervals between tests prevent prompt treatment and should theoretically increase the number of infected children and severity of infection. A study done by the Systematic Review on Congenital Toxoplasmosis (SYROCOT) study group found weak evidence that treatment started within three weeks, compared to treatment started after eight weeks of seroconversion, reduces mother to child transmission, which indirectly suggests that compliance with monthly testing is important. However, the study failed to demonstrate the preventive effect of antenatal treatment on clinical manifestations of congenital infection [10]. Compliance will have to be taken into account in any controlled studies conducted on the benefit of antenatal treatment, as well as in any "real life" applications of their findings.

Several studies will be necessary to understand the reasons for the insufficient testing observed in this study. They will have to take into account the use of other prenatal care programmes and additional socio-demographic and economic variables. The role of insufficient patient knowledge on *Toxoplasma* infection and on its consequences for the foetus should also be investigated. Previous data on primary prevention of toxoplasmosis suggested that French women at risk tend to neglect precautions regarding food and hygiene [11-12]. Linking the number and timing of *Toxoplasma* tests with the patients' daily efforts to avoid infection could help us understand if, or how, both types of prevention interact.

Meanwhile, our study provides several possible directions for improving preventive programmes, particularly those that require patients to make appointments for repetitive examinations. These efforts should ideally be directed towards all actors involved.

Two factors were associated with patients. Receiving free medical coverage was independently associated with a late first test, and with fewer tests overall and longer between-test intervals, indicating continued insufficient access to the health care system or a persistent lack of awareness regarding screening, already widely reported for instance in the 2003 French National Perinatal Survey [5]. Younger patients were also more likely to have a late first test which possibly reflects a lower awareness of standard care offered during pregnancy and a higher proportion of unwanted or belatedly recognised pregnancies. Interestingly, age did not affect the overall number of tests or their regularity, suggesting that factors responsible for the delayed first test were somehow overcome.

Efforts should be made to reach out towards patients who have the least access to information, in order to inform them of the measures to be taken in pregnancy in terms of hygiene and legal and administrative requirements. This information should ideally be given before conception [13-15]. Information on how to avoid *Toxoplasma* infection could be cost-effectively added to messages on other health issues related to young adults (i.e. use of alcohol and drugs, sexually transmitted diseases). Any message promoting an early first serological test would indirectly be a benefit for other areas of antenatal care. Subsequent reminders that testing for toxoplasmosis should be extended to the date of delivery could also be used to convey other information on second or third trimester issues, such as breastfeeding.

Secondly, actions need to be tailored to those who prescribe the tests. In our study, first tests were performed earlier when prescribed by a GP, but subsequent tests were more regular when prescribed by an obstetrician-gynaecologist. As these findings contrast with previous evidence [12-13], further studies are necessary and will need to take into account the adherence of physicians and midwives to recommendations for toxoplasmosis screening, as well as their sex, location and social context, which have been found to play a role in relation to health education and prevention [16-17]. Meanwhile, there is a need to remind GPs, obstetricians and registered midwives of their complementary roles [18]. The biologists performing the tests should also be encouraged to become involved and explain the importance of regular testing to professionals and patients.

The re-use of prescriptions had a positive impact on compliance. The principle of a single prescription covering the entire duration of pregnancy could be promoted as an easy measure. This could even be extended to other biological tests, appointments for medical visits or ultrasound examinations.

Interestingly, the French antenatal prevention programme for toxoplasmosis illustrates well the long-term natural limitations of a programme not supported by a specific campaign. Potential decisions to reinforce it will need to be associated with measures to monitor their effectiveness, and necessary corrections will need to be introduced promptly. However, before taking steps to increase compliance, it is necessary to address the uncertainty surrounding the impact of preventive measures for congenital toxoplasmosis.

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Review articles

EPIDEMIOLOGICAL IMPACT AND DISEASE BURDEN OF CONGENITAL CYTOMEGALOVIRUS INFECTION IN EUROPE

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In Europe, congenital cytomegalovirus (CMV) infection is the leading cause of neurological disabilities in children, causing severe sequelae such as sensorineural hearing loss, neurodevelopmental delay or blindness. The infection causes high disease burden and costs. Nevertheless, there is little awareness of CMV among medical officials and the general public. Although the individual risk of congenital CMV infection is greatest from a primary infection of the mother during pregnancy, maternal non-primary infections also account for a substantial disease burden associated with congenital CMV. Screening programmes for pregnant women and newborns are widely discussed, but have not been implemented by any public health authority in Europe so far. This article gives an overview about a variety of European and other relevant studies regarding CMV seroprevalence, congenital CMV infection and disease as well as screening strategies and preventive approaches.

Primary and non-primary maternal cytomegalovirus infection

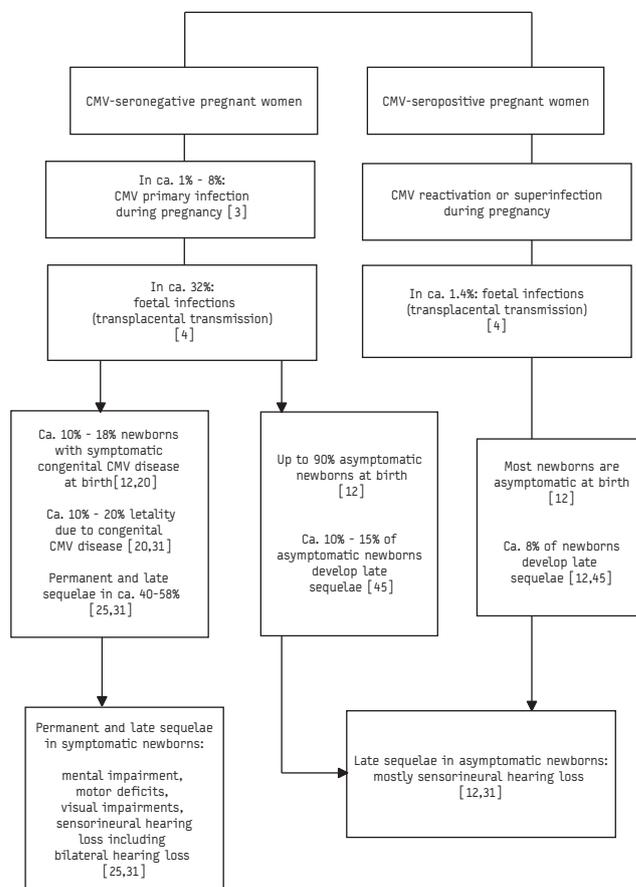
Cytomegalovirus (CMV) is a beta-herpesvirus member of the family *Herpesviridae*. The virus spreads via excretion in nearly all body fluids, such as urine, saliva, vaginal secretions, semen or breast milk. Especially infants and toddlers shed high amounts of virus for months or even years and represent a substantial risk for transmitting the virus to pregnant women by saliva or urine [1]. Sexual transmission of the virus is a common way of infection in adults.

Because the infection in adult immunocompetent individuals is mostly mild or asymptomatic [2], primary CMV infection is rarely diagnosed during pregnancy. The risk of seronegative women to contract primary CMV infection during pregnancy has been reported to be between 1% and 8% [3,4] (see Figure). A force of CMV infection of ca. 0.03 per seronegative women per annum has been found in a British study by Griffiths *et al.* [5].

Viral transmission at the uterine-placental interface can result in congenital CMV infection [6,7] of the foetus or embryo, which can cause congenital CMV disease and permanent sequelae. The risk of CMV disease from intrauterine infection is highest in primary maternal infection. However, in non-primary maternal infections, which results from reactivation of latent CMV genomes or superinfection with new virus strains [8], permanent neurological disabilities or even death of the foetus have been observed [9-11]. In non-primary infection the foetus is thought to be partially protected by maternal immunity and transplacental transmission of immune IgG [12,13].

Multiple studies have determined the rate of vertical transmission in primary and non-primary maternal CMV infection and the development of subsequent CMV disease of the child [9,14-16]. The results of the studies are hampered by difficulties to distinguish between primary and non-primary maternal CMV infection. A metaanalysis by Kenneson *et al.* revealed a transmission rate of 32% in primary maternal infection and a transmission rate of

FIGURE
Frequency of maternal and foetal cytomegalovirus infection and morbidity of infected children



CMV: cytomegalovirus

1.4% in recurrent maternal infection [4]. The Figure shows the frequency of maternal and foetal CMV infection and morbidity of infected children.

Foetal CMV infection and the progression to congenital disease in children

The gold-standard method for prenatal diagnosis of foetal CMV infection is the detection of CMV in amniotic fluid by virus culture or PCR, which is as accurate as and even more sensitive than viral culture [17,18]. False negative results can occur when the test is performed too early after foetal infection, before the foetus sheds virus via the urine [17]. According to the European Congenital Cytomegalovirus Initiative (ECCI), the sensitivity of PCR used to detect viral DNA is very good if amniotic fluid is collected at least six weeks after seroconversion and around the 22nd week of pregnancy [3].

Diagnosis of congenital CMV infection does not necessarily predict later development of congenital CMV disease [19]. Systematic ultrasound is not sensitive enough to detect signs of foetal CMV disease, and most CMV complications can be observed only in the last trimester of pregnancy [3], when interruption of pregnancy is not legally possible in most European countries. Congenital CMV infection during the first trimester is more likely to cause CMV disease, since organogenesis takes place in this period [20,21].

CMV-damage in the foetus may cause spontaneous abortion or prematurity. Cases of congenital CMV syndrome present with an involvement of multiple organs including splenomegaly, hepatomegaly, prolonged neonatal jaundice, pneumonitis, thrombocytopenia, growth retardation, microcephaly and cerebral calcifications. Organ damage is thought to be caused by CMV replication in target organs like the central nervous system of the foetus and indirectly by CMV-induced placental dysfunction [19]. Permanent impairments mostly affect the central nervous system and include progressive hearing loss, spastic tetraplegia, mental retardation and visual impairments [21]. Nearly 14% of children with congenital CMV infection suffer from sensorineural hearing loss (SNHL), and 3-5% of children with congenital CMV infection suffer from bilateral moderate to profound SNHL [22]. About 15-20% of children with moderate to profound permanent bilateral hearing loss were associated with CMV infection, according to a publication by Grosse *et al.* [22].

The majority of congenitally infected children appear asymptomatic at birth, but neurological sequelae may develop after months or even years [23]. Fowler *et al.* report that after a mean follow-up of 4.7 years, 25% of children of mothers with primary CMV infection during pregnancy and 8% of children of mothers with recurrent CMV infection exhibit one or more sequelae [12]. Especially hearing loss may often not be present in the period immediately after birth [24,25]. In a longitudinal study by Dahle *et al.*, 7.4% of 651 children with asymptomatic CMV infection developed SNHL, compared to 40.7% of 85 children born with symptomatic CMV infection [25]. The development of late sequelae accounts for substantial disease burden associated with congenital CMV infection. According to Caroppo *et al.* the costs for prosthesis per child with SNHL that accrued for the Italian public health system in 2005 add up to 260,000 Euro [26].

Although there is evidence for mental retardation in symptomatic children congenitally infected with CMV, the intellectual development of the much larger group of asymptomatic CMV-infected children does not seem to be impaired [27]. A Swedish study failed to detect evidence for intellectual impairment at the age of seven years in a group of children with congenital CMV infection who had shown normal neurological development at the age of 12 months [27].

Seroprevalence of CMV and prevalence of CMV infection at birth in Europe

Prevalence in the mother

The prevalence of CMV infection at birth is related to the CMV seroprevalence in women of childbearing age, with a reported increase of 10% in maternal seroprevalence corresponding to a 0.26% increase in CMV birth prevalence [4]. Multiple studies have shown that the overall CMV seroprevalence in women of childbearing age depends on age, parity, ethnicity and social status, and differs between countries and regions [28,29,30]. A low socioeconomic status is a risk factor for CMV seroprevalence and congenital CMV infection [31,32]. The Table lists studies from several European countries, indicating factors that were found to influence CMV seroprevalence.

A Finnish study showed that the CMV seroprevalence was higher in Helsinki compared to a rural area in the southwest of the country (70.7% versus 56.3%, respectively) [33]. Often, the seroprevalence in immigrants differed from that of the native population: In a study in Ireland, a low seroprevalence of 30.4% was detected in 670 Irish women, whereas 359 non-Irish women living in Ireland showed a CMV seroprevalence of 89.7% [36]. The overall CMV seropositivity can also change over time. In Spain, 66.3% of 2,136 women were found to be seropositive for CMV in 1993, compared to 57.4 % of 2,198 women in 1999 [37,38]. Between 1993 and 1999, the decrease in CMV seroprevalence has been significant in the age group of 31-41 year-olds in this study [37,38]. In pregnant women in Turkey, very high seroprevalences of up to 94.9 % were reported [40,41]. In most European countries, a high socioeconomic status seemed to correlate with low CMV seroprevalence. The IgG antibody prevalence against CMV among pregnant women in Germany was highest among welfare recipients (93%), followed by those covered by statutory health insurance (56.2%), but was only 31.8% in the group of women with private health insurance [35].

Prevalence in the newborn

The prevalence of CMV infection in the newborn at birth depends on diagnostic criteria and the laboratory detection methods used. Some publications define CMV infection on the basis of a positive virus culture in urine or saliva [9,30,42]. In other studies, positive results of PCR assays are used for diagnosis of CMV infection at birth [16]. The sensitivity of CMV-IgM testing in the newborn as basis for birth prevalence estimates is about 25% and can not be recommended [4]. Diagnosis of CMV infection should be performed within two weeks after birth, since later diagnosis does not allow differentiation between congenital and sub- or postpartal CMV infection.

In a Dutch study, CMV infection was diagnosed by positive CMV PCR from throat samples or by CMV culture from urine samples. 7,793 newborns were tested, and the prevalence of CMV infection at birth was 0.9 per 1,000 newborns. None of seven congenitally infected children in this study showed any sequelae in a follow-up

period of 24 months [30]. However, a differentiation between primary and non-primary infection in the mothers of congenitally infected children was only available for two mothers, who suffered from a recurrent CMV infection during pregnancy. The overall CMV seroprevalence of mothers in this study was 41% [30].

A large Swedish study revealed 0.5% congenitally CMV-infected newborns by virus isolation testing. A total of 16,474 newborns were tested, and 29% of the infected children showed transient neonatal symptoms, whereas 18% of the infected children presented with neurological symptoms at the age of seven years [9].

In an Italian study, isolation of CMV from saliva led to diagnosis of congenital CMV infection [42]. Newborns were subdivided in two groups, a group of 185 children with suspected congenital CMV infection and a control group of 1,286 asymptomatic children. In the control group, overall prevalence of CMV in saliva was 0.47%, compared to 5% in the group of children with suspected CMV infection. Two of 15 neonates with congenital CMV infection developed sequelae in the two-year follow-up period and one further neonate died [42]. A meta-analysis by Kenneson *et al.* including 27 studies reported a birth prevalence of congenital CMV of 0.64% (95% confidence interval (CI): 0.60-0.69%) [4]. A further metaanalysis by Dollard *et al.* revealed a birth prevalence of 0.7% and a percentage of 12.7% symptomatic children at birth [31].

In an early African study from 1978, Schopfer *et al.* reported that 1.4 % of 2,032 newborns in Côte d'Ivoire had CMV viraemia,

when screened by viral culture [14]. Two studies recently performed in Gambia (West Africa), which defined CMV infection at birth on the basis of a sensitive nested PCR detection method and screening of urine samples within two weeks after birth, found prevalences of 5.4% and 3.9% [16,43]. Congenital CMV infection was associated with active placental malaria infection [16]. The prevalences of congenital CMV were higher in these studies compared to birth prevalences in industrialised countries [16,43]. Although these African studies may not be directly relevant for European societies in general, it is of interest that in populations with a presumably very high seroprevalence of CMV, about 1.4-5% of infants are shedding CMV at birth due to non-primary maternal infection. A considerable proportion of these children may develop late sequelae and thus contribute to the disease burden of congenital CMV infection. It is therefore important to consider vertical transmission of CMV due to non-primary maternal infection, and similar infection rates may be possible in immigrant communities living in Europe who originated in high-prevalence countries.

Prevention and treatment strategies against congenital CMV infection

Prevention strategies are classified as primary, secondary and tertiary prevention. Primary prevention strategies try to avoid an infection and are mostly accomplished by precautions against exposure to the virus, i.e. hygiene measures and change of behaviour. Secondary prevention strategies allow identifying infected patients at an early stage, with the aim of stopping progression of infection and disease. In the case of symptomatic disease, tertiary

TABLE

Seroprevalence of cytomegalovirus infection in different European countries and influential factors

Country and region	Study	Seroprevalence	Number of study participants	Factors influencing seroprevalence
Finland, Helsinki	[29]	70.7%	1,088 pregnant women	Social environment, low impact of age
Finland, southwestern (rural) Finland	[33]	56.3%	558 parturient women	Parity
France	[34]	51.5%	1,018 pregnant women	Age, parity, place of birth (seroprevalence increasing from north to south)
Germany	[2]	64.4%	9,870 men and women (aged 1 to > 60 years)	Age
Germany	[35]	43.3% in pregnant women with testing initiated by gynaecologist; 47.5% in randomly selected pregnant women	11,572 pregnant women with testing initiated by gynaecologist; 1,033 randomly selected pregnant women	-
Ireland	[36]	30.4% in Irish women 89.7% in non-Irish women	670 Irish women 359 non-Irish women	Immigration
The Netherlands	[30]	41%	7,524 pregnant women (aged 16-47 years)	Ethnicity, socio-economic status, metropolitan area (connected to ethnicity)
Spain	[37]	1993: 66.3% 1999: 57.4%	1993: 2,136 women 1999: 2,198 women (aged two to 60 years)	Age
Spain	[38]	1993-1994: 62.8%	2,030 men and women (aged two to 60 years)	Age
Sweden, southern Stockholm	[39]	72 %	1000 pregnant women	-
Turkey, South	[40]	94.9%	1,652 pregnant women	-
Turkey, West	[41]	96.4%	1,972 pregnant women	-
United Kingdom, London	[28]	45.9% in white women 88.2% in Asian women 77.2% in black women	20,000 women	Ethnic group, parity, age, social class

prevention strategies try to prevent the development of severe sequelae after infection. Prenatal primary and secondary screening strategies as well as postnatal secondary and tertiary screening strategies are widely discussed for congenital CMV disease, but have not yet been implemented by any European country [44,45]. The implementation of screening programmes is hampered by obstacles such as lack of awareness, financial costs and possible deficits in the availability of detection methods.

Prenatal prevention

As a strategy for primary prevention, all pregnant women should be provided with information about the risk of CMV infection and the possible consequences an infection can have for the child. According to a study in the United States (US), not many women are well informed about the risk of CMV infection and congenital CMV disease. Of 643 women surveyed, only 22% had heard of congenital CMV and among a list of common causes of birth defects, women were least aware of congenital CMV [46]. In a national mail survey of the US population, only 14% of female respondents had heard of CMV [47]. Pregnant women, especially those who work with children, should be educated about behaviours that are associated with a high risk of CMV transmission [48].

Close contact with young children is a particular risk factor for CMV transmission, because infected children shed high concentrations of the virus over a long period of time in urine and salivary secretions. In a recent molecular epidemiological study, children were identified as the source of infection for the majority of pregnant women with primary CMV infection [1]. Preventive hygienic measures such as handwashing and avoiding direct contact with potentially contaminated body fluids, are likely to be effective to prevent CMV seroconversion in pregnant women when dealing with infants or toddlers [49]. Nevertheless, unambiguous results from intervention studies showing reduced rates of congenital infections are still lacking.

Another important route of CMV infection in adults is sexual transmission of the virus. A recent onset of sexual activity has been identified as an independent risk factor for congenital CMV infection in the offspring of young women [50]. However, precise data on the relative risk of CMV transmission during pregnancy by a serodiscordant partner are not yet available.

A safe and effective CMV vaccine for seronegative women is not available so far and remains a major public health priority in countries with a high proportion of seronegative women of childbearing age [51,52].

Prenatal screening

Different secondary prenatal screening strategies exist that rely on early detection of primary CMV infection in pregnant women. Most prenatal strategies are based on serological testing during pregnancy. Primary CMV infection may not be diagnosed on clinical grounds, since symptoms such as fever or flu-like symptoms are often mild or misinterpreted, which makes it important to do serological tests for definitive diagnosis. Evidence for primary infection is based on seroconversion of the mother during pregnancy and the detection of low avidity anti-CMV-IgG antibodies which indicate a recent primary immune response.

In a study in Belgium, Naessens *et al.* used a serologic strategy based on testing for CMV-specific antibodies during the first prenatal visit and at birth. This approach identified 82% of newborns at risk for congenital infection and neurosensory sequelae

[53]. Another screening strategy includes testing of maternal CMV antibodies at the beginning of pregnancy and at 20-22 weeks gestation to demonstrate seroconversion in pregnant women with primary infection. Screening during the first trimester allows to determine the approximate date of primary infection by using CMV-IgG avidity tests [3].

In a pilot study undertaken in several Italian regions, routine screening used CMV avidity testing following positive detection of CMV-IgM to detect primary CMV infections. A low avidity of CMV-IgG antibodies suggested a recently acquired primary CMV infection [54]. Nevertheless, positive CMV-IgG testing and the presence of high avidity IgG antibodies do not exclude the possibility of congenital CMV infection of the unborn, since non-primary infection during pregnancy and CMV transmission to the foetus can occur. The serologic screening models may therefore not be appropriate for all pregnant women, especially in populations with high seroprevalence for CMV as seen in some European countries.

Prenatal management and treatment

The management of the pregnancy in cases of primary CMV infection is a matter of debate [23]. Suspected foetal CMV infection most often results in amniocentesis, an invasive test that causes spontaneous miscarriages in about 1% of the cases [44]. The danger of amniocentesis for the foetus needs to be taken into consideration when planning strategies for prenatal diagnosis [44]. When a foetal CMV infection is diagnosed, a decision for elective termination of pregnancy is possible, but difficult because a majority of infected fetuses remain unaffected, i.e. asymptomatic after birth [19]. Diagnosis of CMV infection in the unborn will severely worry most women, and obstetricians might not be able to refuse the request of pregnancy terminations due to the inability of excluding all possible severe sequelae [3].

At present, there is no recommended treatment for pregnant women with CMV infection. The effect of passive immunisation on prevention of congenital CMV infection in clinical trials has been investigated by Nigro *et al.* [55,56]. In a non-randomised prospective study, pregnant women with primary CMV infection received a preparation of human hyperimmune IgG against CMV (Cytotect®). Cytotect® infusion was reported to be associated with a significantly lower risk of congenital CMV infection and disease at birth [55]. These findings remain controversial as the study was lacking a strict randomised protocol [57,58]. The site of action of CMV hyperimmunoglobulin is presumably the placenta, as manifestations of congenital CMV at birth are probably caused in part by virus replication in placental tissue, leading to placental insufficiency [6,7,59].

Nigro *et al.* further reported a regression of foetal CMV-associated cerebral abnormalities following therapy with Cytotect® in individual cases [56]. The sensorial, mental and motor development of these children was normal when evaluated at the age of three to seven years [56]. However, a publication bias favouring those cases in which hyperimmunoglobuline treatment had a protective effect cannot be excluded. Independent controlled studies are needed to evaluate the safety, effectiveness and cost-effectiveness of passive immunisation in women with primary CMV infection during pregnancy. Possible side effects of CMV immune globulin are mainly anaphylactic reactions [51].

Postnatal screening

Screening of all newborns for CMV infection is a postnatal tertiary screening approach. Universal hearing screening at birth by use of otoacoustic emission (OAE) is offered in most European countries and detects symptomatic hearing impairment at birth. However, more than two thirds of cases of hearing loss among children congenitally infected with CMV develop only months or years after birth and may therefore be missed by a hearing screening at birth [3,24]. Screening of all newborns for CMV shedding in the urine and monitoring of all congenitally CMV infected newborns in long-term audiologic follow-ups could improve the identification of children with progressive hearing loss which can become evident as late as at the age of five years or even later [24,60]. Early diagnosis and intervention such as speech therapy, sound amplification or cochlear implants are essential to improve the disease outcome in children with hearing loss. Newborns infected with CMV could also benefit from ophthalmological assessment and neuroimaging for documentation of central nervous system (CNS) disease in the neonatal period [48]. Postnatal screening strategies would allow the identification of risk factors for the development of severe sequelae and an assessment of the disease burden of congenital CMV disease.

The gold-standard to detect congenital CMV infection at birth is viral culture or PCR within the first two weeks of life from urine or saliva. Barbi *et al.* have implemented a nested-PCR test from neonatal dried blood spots on Guthrie cards as a convenient possibility for screening [42,61]. Most importantly, only this approach allows diagnosis of congenital CMV infection retrospectively. For this purpose, storage of Guthrie cards for a minimum of five years must be assured.

Postnatal treatment

Ganciclovir treatment of symptomatic newborns has been evaluated in several studies [62-65]. Kimberlin *et al.* investigated in a randomised controlled study the effect of a six-week therapy with intravenous ganciclovir in under 30 days-old neonates with symptomatic CMV disease involving the CNS [65]. At a follow-up hearing examination at the age of six months, 84% of the babies treated with ganciclovir had improved their hearing or maintained normal hearing between study entry and the age of six months, compared to 59% of controls. At the age of one year, the hearing had deteriorated in 21% of the treated children between study entry and the age of one year, compared to 68% in the control group [65]. According to Kimberlin *et al.* Ganciclovir therapy begun in the neonatal period in children with symptomatic CMV infection involving the CNS prevents hearing deterioration in the first six months of life and may prevent hearing deterioration in the first year of life [65]. Ganciclovir is toxic to the bone marrow, and two thirds of the treated infants in the study by Kimberlin *et al.* suffered from side effects such as significant neutropenia [65]. Recent studies in neonates with symptomatic congenital CMV infection reported that comparable plasma concentrations can be reached by oral administration of valganciclovir and intravenous administration of ganciclovir [66,67]. ECCI currently recommends the use of 6mg/kg intravenous ganciclovir twice daily for six weeks in babies born with CNS involvement and proven congenital CMV infection.

Disease burden and public health aspects

Based on the available data, congenital CMV infection is of major public health significance. Criteria for the prioritisation of infectious diseases in public health have been proposed, such as burden of disease, epidemiological dynamics, information need and health

gain opportunity [68]. Despite the fact that considerable knowledge gaps still exist to date, CMV has been added to a list of infectious pathogens selected for further evaluation of prioritisation [68], particularly in the context of congenital disease.

CMV infection is the leading non-genetic cause of hearing impairment in children. In France, it has been estimated that a number of 480 infants per year experience severe sequelae and a number of approximately 675 infants per year present with hearing loss due to congenital CMV infection [44]. Around 8,000 children with neurological sequelae related to congenital CMV infection per year have been reported in the US [69].

The disease burden of congenital CMV infection is high and similar to that for congenital rubella before the introduction of rubella vaccination [52]. Since congenital CMV affects the very young, it results in long-term morbidity. In the 1990s, the estimated costs associated with CMV disease for the US health care system amounted to at least 1.86 billion US dollars annually, with more than 300,000 US dollars per child [52]. To assess the socio-economic costs of congenital CMV infection and its impact expressed as quality-adjusted life-years in Europe, complete epidemiological knowledge of the prevalence of this disease is mandatory. Further research on preventive measures, therapeutic options and screening methods for congenital CMV infection and subsequent health impairment are worthwhile. The availability of evidence-based preventive and therapeutic options should predetermine the implementation of general screening programmes for congenital CMV infection in European countries.

Given the low awareness of the infection in the general public, the need for information on congenital CMV infection is great. Up-to-date information about congenital CMV infection for both healthcare professionals and the public are provided by ECCI. The ECCI provides recommendations by international and European virologists, epidemiologists, immunologists, obstetricians and paediatricians whose aim is to promote awareness of congenital CMV and support research initiatives into this important infection.

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DRUG USE AND PREGNANCY – CHALLENGES FOR PUBLIC HEALTH

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Problem drug use in pregnancy affects a sizeable population in Europe. A literature review was carried out of articles in PubMed, European Monitoring Centre for Drugs and Drug Addiction publications, and related documents in order to assess public health challenges and possible intervention strategies related to problem drug use and pregnancy in Europe. It revealed the following: Involving pregnant drug users in drug treatment is likely to decrease the chances of pre- and perinatal complications related to drug use and to increase access to prenatal care. Timely medical intervention can effectively prevent vertical transmission of human immunodeficiency virus, hepatitis B virus as well as certain other sexually transmitted diseases, and would allow newborns infected with hepatitis C virus during birth to receive immediate treatment. Pregnancy may be a unique opportunity to also help women with dual diagnosis (substance use combined with mental illness) and enrol them into special treatment and support programmes. Issues related to homelessness and intimate partner violence can also be addressed with appropriate interventions. Treatment and care for pregnant drug users should offer coordinated interventions in several areas: drug use, infectious diseases, mental health, personal and social welfare, and gynaecological/obstetric care.

Background

Problem drug use (defined by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) as “injecting drug use or long duration/regular use of opioids, cocaine and/or amphetamines” [1]) and pregnancy affect a sizeable population in Europe. It is estimated that there are about 1.3-1.7 million problem opioid users in the European Union and Norway [2]. Furthermore, approximately 20% of drug users entering drug treatment and around 34% of opioid users are women (the great majority of whom are of childbearing age) [3], and every year, as many as 6.5-11% of female problem drug users may get pregnant or give birth [4,5]. This suggests that each year there may be as many as 30.000 pregnant women using opioids in Europe, and the number of pregnant women using drugs other than opioids may be equally high. The issue of pregnancy and drug use is important to address because of the associated personal and public health challenges regarding both the mother and the unborn child, especially regarding infections that are common among drug-using populations. In this article, we review some of these challenges: infection with blood-borne and sexually transmitted diseases (STIs, including infections with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), dual diagnosis (substance use combined with mental illness), social and personal welfare and drug treatment,; and assess and summarise possible solutions to alleviate these challenges.

Methods

A literature review of articles in PubMed published in or after 1990 was conducted using the keywords “pregnancy” and “drug use” / “substance abuse”, and specific keywords for each area of interest (e.g. “dual diagnosis”, “homeless” etc.). Articles discussing pregnancy and tobacco or alcohol use without the mention of other drugs were not considered. In addition, when articles were found that were especially relevant to this review, the “Related Articles for PubMed” links were also investigated. Furthermore, EMCDDA publications (annual reports, selected issues, statistical bulletin) with relevant information were included. When the original publication referenced other, non-PubMed or non-EMCDDA publications, those references were also included in this review. While our focus was on pregnant drug users in Europe, some non-European references were included when found relevant. In this paper, we use the terms “drug use” to refer to problem use of drugs other than alcohol or tobacco, and “pregnant drug users” to refer to pregnant women with problem use of drugs other than alcohol or tobacco.

Pregnancy complications linked to drug use

Continued drug use during pregnancy may lead to complications for the foetus, for the newborn, and later during childhood [6,7]. Complications for the foetus include spontaneous abortion, restricted foetal growth, incorrect maternal placentation, compromised foetal well-being and pre-term delivery. The newborn can be affected by low birth weight, postnatal growth deficiency, microcephaly, neurobehavioral problems and drug withdrawal syndrome [8,9]. In addition, behavioural and cognitive problems may arise later in childhood, and children may be affected by the mother’s ongoing drug use [7].

Drug treatment

Lack of appropriate obstetric and neonatal care has been associated with obstetric complications and with poor pregnancy outcomes among drug users [9-12]. Treatment of drug dependence of pregnant drug users therefore involves not only a stabilisation of their health and social situation as drug users, but also offers an opportunity for regular contact with health services, including standard pre-natal care [13]. It is thus important to improve pregnant drug users’ access to, and retention in, drug treatment. Since the 1970s, methadone maintenance has been recommended for opioid dependence in pregnancy [14], although some studies have shown that buprenorphine may offer an advantage over methadone with regard to lower intensity of neonatal abstinence syndrome [15-17]. New guidelines from the World Health Organization (WHO)

confirm the recommendation of agonist maintenance treatment for pregnant opioid users on the basis of the risks and poor outcomes associated with withdrawals [18]. However, the possibility of drug-drug interactions should be kept in mind, and dose adjustments of substitution treatment may be necessary in different stages of the pregnancy [19]. A recent systematic review of psychosocial interventions suggested that contingency management strategies are effective in improving retention of pregnant drug users in outpatient treatment, but failed to assess any effects on obstetrical and neonatal outcomes [20]. Evidence on the effects of home visits by nurses, counsellors or midwives to women with a drug problem is currently insufficient [21]. However, several decades of clinical management of pregnant drug users point to a need to consider the life circumstances of the individual women and apply a case management approach [9,10,13,14,17,19,22].

Infectious diseases

Certain infectious diseases such as HIV, HBV, hepatitis C virus (HCV), and some other STIs, are more common among illicit drug users (especially those who inject) than among the rest of the population, and their early detection is essential to reduce the risk of vertical transmission [2,3]. The prevalence of infectious diseases is also high among pregnant women who use illicit drugs [23]. For example, in a sample of 259 pregnant women enrolled in drug treatment in France in 1998, 63,3% were infected with HCV, 8,9% with HBV, 6,2% with HIV and 1,5% with syphilis [24,25]. While policies vary across countries, standard antenatal care in most European countries today include voluntary screening for infections, which can include HIV, HCV, HBV, syphilis, and STIs such as chlamydia infection, in order to provide early diagnosis and appropriate treatment for the mother and to reduce the risk of mother-to-child transmission [26]. Still, many pregnant drug users, especially those who have infectious diseases that are common among drug users (such as HIV or HCV), may receive suboptimal prenatal care due to difficulties accessing prenatal services [24,27,28]. This is worrying, since strong evidence supports the importance of early diagnosis and the effectiveness of interventions aimed at HIV infected pregnant women, with the reduction of vertical transmission rates to under 1% [29,30].

The risk of vertical transmission of HCV during birth is highly variable depending on HCV RNA viraemia and HIV co-infection: It is below 10% in HIV-negative study populations (1-3% among HCV RNA-negative women and 4-6% among HCV RNA-positive women) and up to 41% in study populations in which about half of the women were also infected with HIV [31-35]. Co-infection with HCV and HIV is also associated with an increased risk of vertical HIV transmission [36,37]. In contrast to preventing HIV infection of the child, no safe and effective prevention method exists to prevent perinatal transmission of HCV [31,34,38]. As no viral RNA is present in the breast milk or colostrum of infected mothers, there is no evidence of transmission of HCV through breastfeeding [32,33]. However, HCV viraemia has been found to be associated with active injection drug use among HIV-HCV co-infected female drug users, perhaps due to re-infection or reactivation of HCV [39]. HCV transmission does not occur through breastfeeding but only during pregnancy or birth. The likelihood of transmission increases with the viral load, which is higher during active injecting drug use. Preventing, reducing or stopping injecting (e.g. through opioid substitution therapy) may therefore be a way to reduce the probability of vertical HCV transmission. In addition, antiviral therapy is indicated for HIV-HCV co-infected women past

the first trimester in order to reduce the risk of both HIV and HCV transmission [40].

Infection with HBV is also common among drug users [2]. The current recommendation to prevent the transmission of HBV from mother to child is to administer to the newborn a combination of anti-HBV immunoglobulin followed by three doses of HBV vaccine [41,42]. WHO recommends the global implementation of childhood hepatitis B vaccination [43]. Still, many European countries (Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden, and the UK) provide immunisation only for at-risk populations, a practice that is debated due to the difficulty of identifying all at-risk individuals [43,44]. Other STIs are also common among pregnant drug users [45]. As bacterial STIs (e.g. syphilis, gonorrhoea, chlamydiosis) can readily be treated with antibiotics, which also prevent vertical transmission [46,47], screening for STIs and treatment of those who are infected are recommended for pregnant drug users.

Psychiatric co-morbidity

Dual diagnosis, i.e. co-morbidity of substance abuse and mental illness, is common among both drug using and mentally ill populations [48]. In Europe, as many as 80% of clients enrolled in drug treatment report a mental health problem [2,49-52]. Psychiatric co-morbidity is complex because patients may suffer from more severe symptoms than people with only substance use or mental illness, they may not respond well to treatment, and, when in treatment, they may have higher rates of relapse and attrition [53,54]. While in the general population men report higher levels of drug use than women [55], women report higher rates of mental illnesses, especially depression and anxiety disorders [56]. However, levels of psychiatric co-morbidity among substance users seem to be similar in both sexes [57]. Little is known about pregnant women with a dual diagnosis. In a study in France, 22% of pregnant drug users in substitution treatment for opioid use reported moderate to severe psychiatric disorders, mostly depression, neuroticism and anxiety disorders [25]. Pregnant women suffering from psychiatric co-morbidity often report a history of emotional, physical and sexual abuse as well [57,58]. Pregnancy may be an opportunity of contact with care services for both conditions of co-morbidity. However, the fear of losing the custody of the child and the feeling of guilt about using drugs during pregnancy may often pose a barrier to seeking treatment [57]. Interventions among pregnant women with psychiatric co-morbidity should target the three problematic areas (mental health, drug related problems and pregnancy) in a co-ordinated and integrated way, taking into account the individual needs of these women [10,19,59].

Social and personal welfare

Issues related to the social and personal welfare of pregnant drug users include, among other things, homelessness and intimate partner violence. Overall, about one in ten drug users entering treatment in Europe lives in unstable conditions or is homeless [3]. Homelessness and drug use in pregnant women are associated with problematic perinatal events [11,12], inadequate access to health care, social isolation, and psychosocial and physical problems [60]. Among female drug users, those who are homeless more often face difficulties obtaining public assistance, and are afflicted by greater social isolation, a lack of family and social networks, higher rates of emotional, physical and sexual abuse as well as under-nutrition, and they are more likely to engage in survival sex [60]. Some homeless female drug users may be able to discontinue the

use of those drugs on which they are not dependent, but they may maintain the use of their main drug (most often crack cocaine or heroin) [57]. Homeless pregnant drug users are less likely to seek drug treatment than domiciled pregnant drug users, and, when in treatment, they are less likely to maintain abstinence and are more likely to leave treatment prematurely [60].

Many women are victims of intimate partner violence [61,62]. When compared to women who have not experienced assault, pregnant women who have been assaulted were more likely to drink alcohol or use drugs [63,64]. In a perinatal substance abuse treatment clinic, many pregnant drug users reported being abused during their pregnancy: 41% reported emotional abuse, 20% physical abuse and 7% sexual abuse [65]. Abused pregnant drug users often report that emotional abuse is more disturbing than physical abuse, and many report being subject to both emotional and sexual abuse [64,65]. The abuser in most of the cases is the partner, ex-partner or someone closely related to the victim [65-67]. The risk of increasing drug or alcohol use increases after experiencing violence [63,65,67]. Intimate partner violence among pregnant drug users is responsible for health problems such as depression, post-traumatic stress disorder, chronic pain in different parts of the body (e.g. in the abdomen), gastrointestinal and gynaecological problems [63,65-67]. Clinics, including prenatal clinics and drug treatment centres, may be the most appropriate place for pregnant drug users to receive interventions in order to prevent recurring partner violence and abuse [62,68-70].

Conclusions

Pregnant drug users are at a higher risk than pregnant women who do not use drugs of contracting blood-borne and sexually transmitted infections. In addition, they are also affected by a number of physical, mental and social health problems. Services geared towards the general population need to cater to pregnant drug users as well. Special services for problem drug users should use outreach methods to timely identify pregnant drug users not in contact with services and ensure referral and collaboration with pregnancy care givers, using integrated case management strategies. Treatment and care for pregnant drug users should offer coordinated, multidisciplinary interventions encompassing several areas: prevention, screening and treatment of infectious diseases; mental health; personal and social welfare; gynaecological/obstetric care; and drug use [20,21]. The aim of such treatment and care is to reduce risk through the integrated collaboration of obstetricians, addiction counsellors, social workers, general practitioners, and other health care specialists [71], and to link drug treatment with other interventions aimed to help pregnant drug users. In addition, to prevent parental neglect that may be the consequence of drug abuse, adequate parenting support services should be made available and easily accessible to pregnant drug users.

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Meeting reports

THE 2008 CONGENITAL CYTOMEGALOVIRUS CONFERENCE, 5-7 NOVEMBER, CENTERS FOR DISEASE CONTROL AND PREVENTION, ATLANTA

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The theme of this conference was “public health action towards awareness, prevention, and treatment”. The purpose was to bring together researchers and clinicians from various fields to discuss the latest research on congenital cytomegalovirus (CMV) infection and how these findings can be translated into public health action for better health of women and children. In addition, families with children affected by congenital CMV participated in the conference, either in integrated sessions together with the experts or in separate sessions only for the families. These children were a testimony of the severe disabilities that congenital infections can cause.

More than 250 participants from all over the world attended the conference, which included about 50 oral presentations and 50 poster presentations. In this report the different topics of this conference will be briefly discussed, with a focus on disease burden and public health. Most presentations can be found at: <http://www.congenitalcmv.org/cmvsides2008.htm>

Epidemiology

Michael J. Cannon (United States (US) Centers for Disease Control and Prevention (CDC)), one of the organisers of this conference, described three areas of recent epidemiologic studies at the CDC.

- CMV awareness among women and obstetrician/gynaecologists,
- Seroprevalence data leading to an understanding of transmission modes on a population level,
- Studies on the overall burden of congenital CMV infection and disease and the particular burden due to permanent, bilateral hearing loss.

These studies are intended to identify women who are at high risk of giving birth to children with congenital CMV and likely to profit from antiviral treatment or other interventions, and to clarify what messages need to be communicated about congenital CMV prevention. Studies on the prevalence of CMV infections in general show that CMV seropositivity is highly determined by racial/ethnic factors and seropositivity of siblings and mother. CMV infections during pregnancy occur in about eight of 1,000 pregnancies. Most of these congenital CMV infections occur in previously seropositive mothers [1]. Between 17 and 20 % of these congenitally infected children will have permanent disabilities [2].

Karen B. Fowler (Department of Paediatrics, University of Alabama at Birmingham, US) showed that new developments in

diagnosing and treating CMV infections, as well as an emerging interest from the US Newborn Hearing Screening Community for the identification of CMV-related hearing loss, has resulted in a need to reconsider surveillance or screening programmes for congenital CMV infection.

Suzanne Luck (Royal Free and University College Medical School, London, United Kingdom (UK)) reported on a newly developed CMV-related treatment registry of pregnant women and infants in the UK that is currently being extended to the rest of the European Union (EU).

Postnatal treatment and follow-up

The benefits and risks of current antiviral treatments for children with congenital CMV were presented by David Kimberlin (University of Alabama at Birmingham, US). Data on the treatment of congenital CMV are only available for babies that are born symptomatic. In this group, administration of intravenous ganciclovir for six weeks protected against hearing deterioration. Recently, it has been demonstrated that administration of an oral solution of valganciclovir resulted in similar blood concentrations of ganciclovir as intravenous administration of ganciclovir. A new multicenter study conducted by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group is now evaluating whether six months of oral valganciclovir therapy results in better hearing and neuro-developmental outcomes than six weeks of oral valganciclovir therapy.

The long-term sequelae of congenital CMV on hearing loss and brain development were discussed by John Eichwald (US CDC) and Ira Adams-Chapman (Emory University, Atlanta, US).

Pathogenesis and immunology

In this session, an up-date was given on the latest insight into the pathogenesis of congenital CMV and the immunological responses to this infection. Lenore Pereira summarised several studies on the pathogenesis of intra-uterine infection and the histopathological effects on the uterine-placental interface, such as villous inflammation, fibrosis and necrosis. Immunostaining revealed expression of proteins associated with hypoxia. These results suggest direct viral damage resulting in placental hypoxia. She also showed that treatment with intravenous hyperimmunoglobulin, a recently reported intervention in women with primary CMV infection, resulted in compensatory vascularisation of the placenta and villous

regeneration. Another presentation showed that a murine model that had previously been used to study the pathogenesis of CMV infection has now been used to study hearing loss.

Awareness and behavioural interventions

The main message of this session was that only few women have heard of congenital CMV, and although studies have shown that prevention is possible by adopting certain hygienic behaviours, most women were not informed by their obstetricians or gynaecologists about the risks of CMV infection and about possible hygienic measures. Information on the internet regarding CMV prevention is also lacking.

On the other hand, if counselling is applied, women are motivated to be screened for CMV IgG antibodies and to apply hygienic measures.

Prenatal diagnosis, prognostic indicators, correlates of immunity, and treatment

Maria Grazia Revello (Servizio di Virologia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy) focused on recent developments in prenatal diagnosis. The main diagnostic methods are immunological detection of infection in the mother, detection of viral DNA and marker proteins in foetuses, and ultrasound examination. These methods have greatly improved the possibility of counselling pregnant women. Not only can infected foetuses at increased risk of congenital disease be identified more reliably, they also allow more efficient monitoring of the effect of newly described interventions, such as CMV hyperimmunoglobulins and valganciclovir.

Recently, administration of hCMV-specific immunoglobulin has been reported to spectacularly reverse the prognosis in severely affected foetuses [1]. Maria Grazia Revello announced that a multicenter randomised, double blind, placebo-controlled trial in pregnant women with primary CMV infection will start in Italy. The trial will concentrate on the prevention of mother-to-child transmission by administration of hCMV-specific immunoglobulin.

A comparable trial was presented by a second speaker, Mara Dinsmoor from Evanston Northwestern Healthcare.

Stuart Adler summarised in his lecture the findings from CMV hyperimmunoglobulin trials and proposed guidelines for treatment and monitoring. More treatment options may be underway, as an orally active analogue of cidofovir was shown to be effective in limiting CMV infection in a guinea pig model.

This session was concluded by an interesting discussion on the advantages and disadvantages of prenatal screening. The general opinion of the experts was that previous obstacles to prenatal screening, such as limited knowledge on the foetal outcome, the lack of reliable prenatal diagnostics and of intervention possibilities, have now been overcome. It is time to consider a well-designed prenatal screening programme.

Vaccines

For several years now, developing a vaccine for CMV has been regarded as a top public health priority for the US because of the frequency of congenital CMV infection and its impact on sensory, cognitive and motor disability in children. In this session, the many efforts towards vaccine development, the results in animal models and the first results in phase II trials were presented.

Robert Pass (University of Alabama at Birmingham, US) focused on a CMV glycoprotein B (gB) vaccine. A recent phase II clinical trial showed an overall vaccine efficacy of 50%. Rajiv Khanna (Australian Centre for Vaccine Development, Herston, Australia) showed the results of pre-clinical testing of a novel chimeric vaccine based on a replication-deficient adenovirus which encodes, as a contiguous polypeptide, the extracellular domain of the gB protein together with multiple major histocompatibility complex (MHC) class I and II-restricted T cell epitopes of CMV. CMV-specific CD8+ and CD4+ T-cellular as well as humoral immune responses were induced by this vaccine.

All speakers in this session and roundtable discussion emphasised that although pre-clinical and clinical vaccine studies show promising results, many questions still remain to be answered: What do we want to achieve with a vaccine? What will be the target population? What is the best immune correlate of protection? Which animal model can be used?

Newborn screening

While political and ethical questions remain to be resolved, this session showed that neonatal screening for congenital CMV on dried blood spots (DBS) is technically possible with high sensitivity and in a high throughput fashion. Several speakers emphasised that laboratory testing should be validated thoroughly in order to achieve this high sensitivity. Alternative materials (dried urine or saliva) were shown to be suitable for diagnosing congenital CMV with probably higher sensitivity than DBS testing. However, these materials are currently not usable on a routine basis.

Scott Grosse (National Center on Birth Defects and Developmental Disabilities, US CDC) pointed out that evidence of safe and efficacious treatment is probably crucial if a public health case is to be made for universal screening with DBS.

General conclusions

Considerable progress has been made in the field of congenital CMV. Knowledge is increasing on virus transmission and pathogenesis of congenital CMV, diagnostic algorithms are designed, and prenatal and postnatal intervention strategies are being evaluated.

However, despite the high disease burden of congenital CMV, public awareness is extremely low. Continued research in this field is needed for the development of preventive and therapeutic strategies that will have a high impact on the quality of life of many children worldwide.

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WEB-BASED INFORMATION ON INFECTIOUS DISEASES DURING PREGNANCY – INFPREG IN SWEDEN

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A non-commercial website containing multidisciplinary information on infectious diseases during pregnancy – INFPREG provides information in Swedish for experts and the general public on ante-/peri-/postnatal care [1]. The site, which has been running for 10 years now, intends to meet the need for up-dated information on the relevance of infectious diseases in pregnancy. It is divided into two sections, one for health professionals and one for the general public. Of 35 chapters, 33 provide specific information on various pathogens, and two chapters provide information on screening programmes and on vaccinations. Information presented in each chapter is the result of collaboration of experts from various fields: obstetrics, infectious medicine, paediatrics, clinical microbiology (virology, bacteriology and parasitology), neonatology, epidemiology, hospital hygiene, audiology, ophthalmology. For professionals, the website offers an interactive questions and answers facility. Questions are answered within three working days, and both are stored in a password-protected archive. The site adheres to AMA (American Medical Association) web site guidelines [2].

The chapters dedicated to health professionals include information on the nature of the causing agents, on contagiousness and transmission in society, on the clinical profile in general and in pregnant women, in the foetus and the newborn, on transmission risks, on laboratory methods, diagnosis of infection in the mother and in the foetus/child, on prophylaxis, on therapy, etc. The information available to the general public has essentially the same content but is presented in a more accessible form, and antenatal care centres in Sweden inform pregnant women about the INFPREG site.

INFPREG has so far been a success. The use of the site increased gradually among midwives, obstetricians and the public, with the number of visits increasing from 52,200 in 2002 to 265,000 in 2008. The website is also used in neighbouring Nordic countries, where the epidemiology, vaccination strategies and guidelines are similar to those in Sweden.

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