

**NOVES APORTACIONS
A LA VIGILÀNCIA,
PREVENCIÓ I CONTROL
DEL VIH I D'ALTRES INFECCIONS
DE TRANSMISSIÓ SEXUAL
A CATALUNYA**

**Tesi Doctoral
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5. RESULTATS

5.1. Article 1

Unlinked anonymous testing to estimate HIV prevalence among pregnant women in Catalonia, Spain, 1994 to 2009

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RESUM

Introducció: El seguiment de la prevalença del VIH en la dona embarassada és una de les prioritats de salut pública. L'objectiu del nostre estudi fou estimar aquesta prevalença tant a les dones que tenen el fill com a les que voluntàriament decidiren acabar el seu embaràs. Una de les estratègies per estimar aquesta prevalença és mitjançant el cribratge anònim no relacionat.

Mètodes: Es recolliren mostres per la detecció d'anticossos anti-VIH a partir de tres clíniques on es fa la interrupció voluntària de l'embaràs i del Programa de Detecció Neonatal de metabolopaties que té una cobertura del 99% dels nadons vius a Catalunya. El càlcul de la grandària fixà una mostra del 50% de tots els nadons vius, i en el total de les interrupcions voluntàries realitzades a les tres clíniques. Aquestes mostres es recullen cada dos mesos per tal de corregir possibles biaixos de temporalitat. Dues mostres de sang foren recollides en paper secant (Scheilcher and Schuell no.903TM, Dassel, Germany) i emmagatzemades a 4°C de temperatura fins a la seva utilització. Els anticossos foren determinats utilitzant el test d'aglutinació modificat Serodia IgG (GACPAT) per VIH-1 (Fujirebio Diagnostics). La reconfirmació de les mostres positives fou realitzada a l'Hospital Universitari Germans Trias i Pujol utilitzant el mètode ELISA per VIH-1 i VIH-2. La prevalença anual es calculà considerant el nombre de mostres positives sobre el total de mostres analitzades, amb un interval de confiança del 95%. Les tendències foren analitzades utilitzant el test de Cochran-Armitage. Per la variable edat, la comparació de la prevalença entre les que donaren a llum i les que

interromperen l'embaràs es va fer mitjançant el test no paramètric U de Mann-Whitney. Per a l'anàlisi estadística es va utilitzar Stata SE 8.

Resultats: En el període 1994 a 2009, es van testar per la infecció del VIH, 549.689 dones embarassades que van tenir els seus fills en algun dels hospitals de Catalunya i en el període 1999 a 2006, 31.904 dones que interromperen el seu embaràs. La prevalença de VIH de les que van donar a llum va disminuir de 3,2 a 1,7 per 1000 ($p < 0,01$). També va disminuir en les dones que interromperen l'embaràs, de 2,3 a 1 per 1000 ($p < 0,01$). La mitjana d'edat de les dones embarassades estudiades fou de 30 anys i no hi ha diferències entre les dones infectades pel VIH (30,8 anys) i les no infectades (30,3 anys). No obstant, quan estratifiquem per lloc de naixement de les mares, tot i que només disposem d'aquesta informació per al període 2002 a 2009, les nascudes fora d'Espanya són més joves (29 anys) que les espanyoles (33 anys) ($p < 0,001$). L'evolució de la prevalença segons grups d'edat mostra una tendència decreixent en les dones de 20 a 29 anys mentre que en la resta de grups (igual o bé $<$ a 20, de 30 a 39 i igual o superior a 40 anys) no mostren cap tendència. L'evolució de la prevalença de VIH segons lloc de naixement de les dones que van donar a llum a Catalunya també mostra diferències significatives. Entre 2007 i 2009, la prevalença de VIH a les dones estrangeres augmenta de 1,6 a 3 per 1000, mentre que a les dones espanyoles disminueix de 1,3 a 1,1 per 1000. Entre els anys 2004 i 2009, les dones nascudes a l'Àfrica Sub-Sahariana mostren una prevalença més alta, arribant a 6,9 per 1000 a l'any 2004 i 5,4 per 1000 a l'any 2009.

Conclusions: Des de principis dels anys 90, Catalunya comparant amb les altres regions d'Espanya de les quals es disposa de dades, és una de les regions amb més altes taxes de prevalença de VIH a la població general, després de les Illes Canàries i Balears. Això justifica el seguiment de la prevalença a la dona embarassada. El cribratge anònim no relacionat, comparat amb la política de cribratge universalitzat a totes les consultes prenatales, és més senzill. Per estimar la prevalença del VIH a la dona embarassada, el denominador del cribratge anònim no relacionat és el total de mostres analitzades procedents del Programa de detecció de metabolopaties amb una altíssima cobertura poblacional i ja disponible a l'actualitat. Mentre que el denominador, resultant de la política de cribratge universalitzat a les consultes prenatales, seria el nombre de tests realitzats en aquestes consultes, dada que no està disponible a l'actualitat. Per tant, donada la seva simplicitat i economia, el cribratge anònim no relacionat és adequat pel seguiment de la prevalença del VIH a la dona embarassada a Catalunya.

Unlinked anonymous testing to estimate HIV prevalence among pregnant women in Catalonia, Spain, 1994 to 2009

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This paper estimates the prevalence of human immunodeficiency virus (HIV) infections in women giving birth and women voluntarily terminating pregnancy over a period of sixteen years in Catalonia. Samples for HIV antibody detection were collected from the Neonatal Early Detection Programme for congenital metabolic diseases that covers 99% of infants born in Catalonia. The sampling method collected information of 50% of births every year and of all women attending three clinics for voluntary interruption of pregnancy. Using two sequential immunoassays we analysed unlinked anonymous blood spot samples from 549,689 newborns between 1994 and 2009 and from 31,904 women who voluntarily interrupted pregnancy between 1999 and 2006. HIV prevalence among women giving birth decreased from 3.2 per 1,000 in 1994 to 1.7 per 1,000 in 2009 ($p < 0.01$) and the mean age of infected mothers increased from 26 years in 1994 to 32 years in 2009 ($p = 0.001$). A decrease in HIV prevalence was also observed in women voluntarily terminating pregnancy, from 2.3 per 1,000 in 1999 to 1.0 per 1,000 in 2006 ($p < 0.01$). In contrast, estimated HIV prevalence in mothers born outside Spain increased from 2.2 per 1,000 in 2002 to 3 per 1,000 in 2009 ($p < 0.01$) and their average age increased from 27 years in 2003 to 31 years in 2009 ($p < 0.01$).

Introduction

Accurate estimates of the number of individuals living with human immunodeficiency virus (HIV) infection are essential for the planning and monitoring of HIV prevention and care programmes. Studies of HIV prevalence in sentinel populations are one of the key strategies to monitor the epidemic [1], and one of the methods that has been widely used in sentinel populations is unlinked anonymous testing (UAT) [2]. By 1987, the United States and the United Kingdom (UK) had already put in place UAT programmes to improve the understanding of the evolving epidemic in their

countries. Over the years, UAT in pregnant women has been substituted by regular antenatal screening programmes in most European and North American countries and only few countries such as the UK and Spain still maintain this surveillance approach.

The UAT to monitor trends of HIV infection in women giving birth in Catalonia is performed annually on blood samples collected from newborns. The presence of HIV antibodies in the newborn reflects maternal infection due to the passive transfer of maternal antibodies to the infant. Since this testing is unlinked (prior to HIV testing the link between the specimen and the personal identifying information is removed) and anonymous (the health staff cannot identify an individual's test result), it is impossible to inform the women of the test results.

The use of sentinel populations to estimate prevalence is a common practice and UAT in these populations has been seen since the beginning of its use as a good tool to prevent participation bias associated with populations at risk (the higher the risk the lower the will to participate) [2]. Catalonia UAT has proven to be an easy and cost-effective tool to monitor prevalence because of its association with other screening programmes that provide very good coverage of the population of women of childbearing age. The objective of this study was to describe the HIV epidemic and trends in women giving birth and those terminating pregnancy as an estimation of the HIV prevalence in pregnant women in Catalonia.

Methods

In the period from 1994 to 2009, we used samples from newborns of women living in Catalonia collected as part of an annual cross-sectional study. In addition, we analysed blood samples from women voluntarily terminating their pregnancy in three selected clinics in Catalonia in the period from 1999 to 2006.

Women giving birth

The Catalan Neonatal Early Detection Programme (NEDP) has been collecting blood spot samples from all newborns since 1994. These samples are used to determine hypothyroidism, phenylketonuria and cystic fibrosis in newborns. This screening is carried out annually by the Institute of Clinical Biochemistry (Institut de Bioquímica Clínica, IBC) and covers 99% of all infants born in Catalonia [3].

For 1994, we obtained samples for HIV antibody detection from this pool of the NEDP for the period between August and December. For all subsequent years until the end of 2009, we selected samples from every second month. The total sample obtained represents half of the yearly newborns in Catalonia [4].

Before determination of HIV antibody status, the samples from women giving birth were screened for neonatal metabolic disease. The remaining dried blood spots were used for the HIV antibody detection. This is an UAT programme to estimate HIV prevalence in pregnant women. Although this meant that the women could not be informed of the result, all of them were offered HIV testing as part of their routine screening during pregnancy, and women testing positive there were offered treatment. The annual number of samples needed to estimate a prevalence of between 1.8 and 2.8% with a 95% confidence interval and a precision of 0.06% is around 35,000 samples. The yearly mean of samples obtained during our period of study was 34,391 [5].

Women terminating pregnancy

The second source of information to monitor HIV prevalence in pregnant women were blood samples taken from women attending three specialised medical centres to terminate their pregnancies. Informed consent was required to obtain these samples. All dried blood spots from women terminating pregnancy were sent to the IBC for HIV antibody detection.

There were at least 11,000 voluntary interruptions of pregnancy annually in the three centres participating in the study. Testing all samples from these centres, we can therefore estimate a prevalence of 2 per 1,000 with a 95% confidence interval and a precision of 0.08%.

In women terminating their pregnancy, information on age was available for those sampled in the years 1999 to 2006. Mean age comparisons between women giving birth and those terminating pregnancy have been performed for this period of time. Information about country of origin was poor and discarded in the analysis of this set of samples.

Sample analysis

Sample collection and HIV antibody detection was done using dried blood spots. Two drops of blood were collected on filter paper discs (Schleicher and Schuell no. 903TM, Dassel, Germany) and stored at 4 °C until used. HIV antibodies were determined using a

modified Serodia IgG antibody-capture particle agglutination test (GACPAT) for HIV-1 (Fujirebio Diagnostics) [6]. Positive samples were sent to the Microbiological Service of the University Hospital Germans Trias I Pujol (HUGTIP) to confirm the results using an IgG antibody capture ELISA for HIV-1 and HIV-2. Until 2001 this was done using the GACELISA test (Murex, UK) [7]. In 2002 this confirmatory test was replaced with the Pasteur HIV-1/2 GenElavia Mixt ELISA (BioRad, Spain) after checking that normal and external valid values were similar for both tests [8].

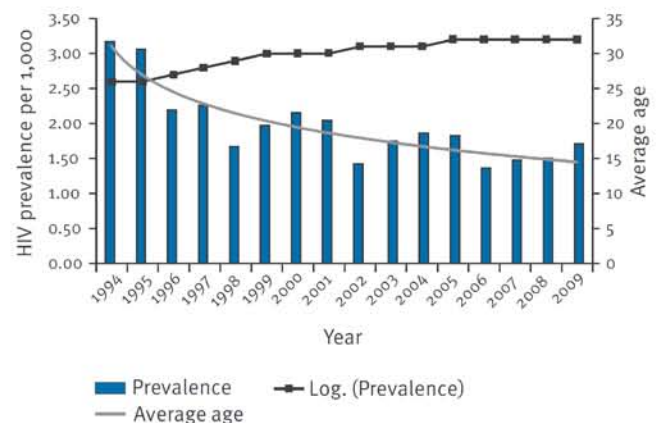
Variables collected in the study were HIV status of the pregnant women, age and country or region of origin. Confidentiality for both data sets (women giving birth and those terminating pregnancy) was ensured by using a computer-aided coding process at the NEDP. The results of HIV antibody testing could not be correlated with any patient identification number.

The annual HIV prevalence among women of child-bearing age was computed as the number of HIV-positive samples divided by the total number of HIV-positive and HIV-negative samples tested each year, with 95% confidence intervals. Trends were analysed using the Cochran-Armitage test. Data were analysed using Stata SE 8. For the age variable, a comparison between women giving birth and those terminating pregnancy was done by non-parametric Mann-Whitney U-test.

Results

Among the 581,593 blood spot samples analysed, 549,689 were from infants born during the years 1994 to 2009 and 31,904 from women terminating their pregnancy during the years 1999 to 2006. We obtained 1,081 HIV positive results, representing a global prevalence of 1.85 per 1,000. Overall, we tested 54% of all women giving birth in Catalonia, ranging from 53% in

FIGURE 1
HIV prevalence in women giving birth, Catalonia, 1994–2009 (n=549,689)



HIV: human immunodeficiency virus.

1996 to 46% in 2008, and 24% of those terminating pregnancy from 1999 to 2006.

Our estimates show a decreasing trend in HIV prevalence from 1994 (3.2 per 1,000) to 2002 (1.4 per 1,000; $p < 0.01$). It then remains steady until 2009 (1.7 per 1,000; $p = 0.145$) (Figure 1).

Information on age was available in 562,977 of 581,593 samples (97%). The mean age for all women was 30.3 years, similar in HIV-seropositive (30.8 years) and HIV-seronegative women (30.3 years). However, the mean age of HIV-infected mothers was lower among those born outside Spain (29 years) than among Spanish mothers (33 years) ($p < 0.001$), reflecting the mean age of the general population: mean age of foreign and Spanish mothers, 29 years and 32 years, respectively.

When analysing the data by age, we saw a decreasing logarithm trend in the age group of 20 to 29 year-olds ($p < 0.001$) and no significant trend in the age groups under 20 years ($p = 0.41$), from 30 to 39 years ($p = 0.04$) and 40 years and older ($p = 0.01$) (Figure 2).

HIV prevalence in women giving birth by country or region of origin

Country of birth information was available only for women giving birth between 2002 and 2009, with poor completion in 2002 (country of origin was unknown in 79% of records) but much better completion in 2009 (missing information in only 2% of the records).

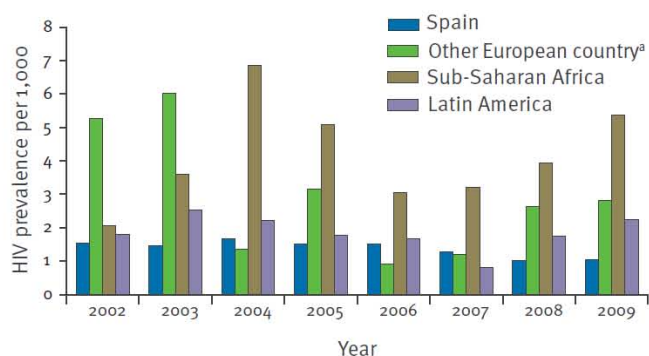
We observed an increasing trend in HIV prevalence between 2007 (1.6 per 1,000) and 2009 (3 per 1,000) among women born abroad, compared to lower prevalence rates and a decreasing trend from 1.3 per 1,000 to 1.1 per 1,000 among Spanish women in the same period. Prevalence was particularly high among those from Sub-Saharan Africa, reaching 6.9 per 1,000 in 2004 and 5.4 per 1,000 in 2009 (Figure 3).

HIV prevalence trends in women terminating pregnancy versus those giving birth

Information on women terminating pregnancy was available only for the period 1999 to 2006. We analysed samples from 31,904 women who interrupted their pregnancy in the three participating centres, representing 27% of all women who legally interrupted pregnancy in Catalonia.

FIGURE 3

HIV prevalence trends in woman giving birth, by country or region of origin, Catalonia, 2002–2009 (n=315,657)

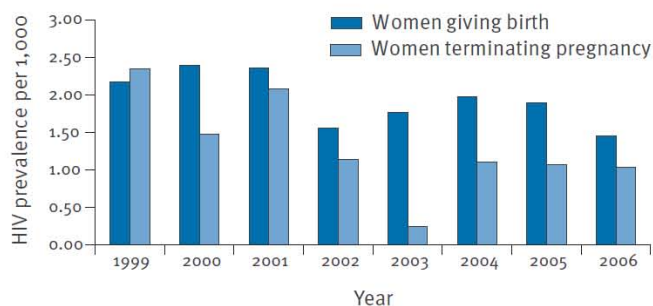


HIV: human immunodeficiency virus.

^a European Union plus European Free Trade Association countries.

FIGURE 4

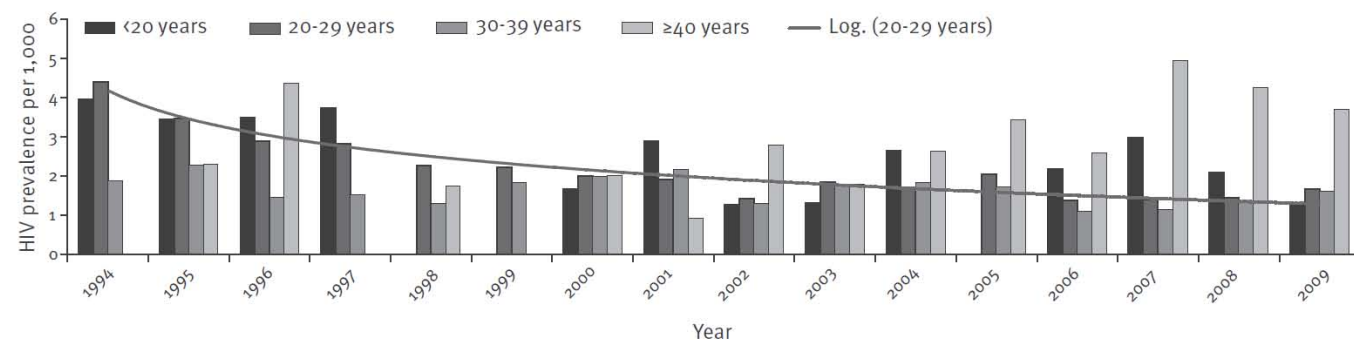
HIV prevalence in women terminating pregnancy versus those giving birth, Catalonia, 1999–2006 (n=325,223)



HIV: human immunodeficiency virus.

FIGURE 2

HIV prevalence in women giving birth, by age, Catalonia, 1994–2009 (n=549,689)



HIV: human immunodeficiency virus.

HIV prevalence during this time period did not differ between women terminating pregnancy and women giving birth ($p=0.06$), with 42 of 31,904 (13%) and 522 of 293,120 (18%) HIV-positive samples, respectively. HIV-positive women terminating pregnancy were younger than those giving birth (average age 26.6 versus 30.6 years; $p<0.0001$) for the same time period. A non-significant decreasing trend in HIV prevalence was observed in women who voluntarily interrupted pregnancy ($p=0.066$) from 2.3 per 1,000 in 1999 to 1.0 per 1,000 in 2006 (Figure 4).

Discussion and conclusion

Unlinked anonymous surveillance of newborns and women interrupting pregnancy allowed us to estimate the HIV prevalence among pregnant women as a surrogate for HIV infection prevalence in women of child-bearing age. We found this method to be feasible and reliable in Catalonia. Our study provides 16 years of meaningful information, if limited by covering only the variables age and country of origin.

Data from women voluntarily interrupting pregnancy were included with the objective of identifying any potential bias due to voluntary interruption of pregnancy among women with higher rates of HIV infection [9]. However, their HIV prevalence was similar to the one found in women giving birth. Nevertheless, the small sample studied cannot guarantee the representativeness for all interrupted pregnancies performed in

Catalonia, because important hospitals did not contribute data.

The HIV prevalence rates followed a decreasing trend between 1994 and 2002, rose in the following three years (2003 to 2005), dropped in 2006 and then increased again in the years up to 2009. This rise was observed not only in Sub-Saharan African mothers but also in other European countries and Latin America. As expected, the seroprevalence observed in this study reflected the prevalence in the regions where the study population originated. For the decade 2000 to 2010, the HIV prevalence in Sub-Saharan Africa is reported as around 50 per 1,000, in Latin America around 5 per 1,000 for the same time period and in other European countries of around 2 per 1,000 [10,11].

Compared to other autonomous regions of Spain for which data are available, Catalonia has since the early 90s had one of the highest HIV prevalence rates [12,13], after the Canary and Balearic Islands. Over the period from 1995 to 1998 prevalence rates we observed in Catalonia decreased from 3.1 to 1.7 per 1,000. Other European countries such as Germany, Italy and the UK, where UAT has been used since the early 1990s, had different experiences in the same time period. In Italy [14,15] rates did not change significantly as well as in Scotland [15] and Germany [15].* Information available from the years 1999 to 2004, shows that HIV prevalence estimations from UAT in Catalonia followed a

TABLE**

HIV prevalence rates per 1,000 samples tested from unlinked anonymous testing in some European countries

Year	Catalonia (Spain)	Spain	Germany	Italy	Scotland (UK)	UK (all)
1995	3 ^a	1 ^a	NA	0.9 ^b	NA	NA
1996	2.2 ^a	1 ^a	NA	0.7 ^b	NI	NA
1997	2.2 ^a	1.3 ^a	NA	0.6 ^b	NI	NA
1998	1.7 ^a	1.4 ^a	NA	0.8 ^b	NI	NA
1999 ^c	2	1.6	0.2	0.8	0.2	0.7
2000 ^c	2.2	1.3	0.2	-	0.5	0.9
2001 ^c	2	1.4	0.3	0.8	0.3	1.1
2002 ^c	1.4	1.6	0.2	0.7	0.6	1.5
2003 ^c	1.7	1.6	NA	NA	0.3	1.7
2004 ^c	1.9	1.5	NA	NA	0.5	1.9
2005	1.8 ^d	1.3 ^d	NA	NA	NA	NA
2006	1.5 ^d	1.7 ^d	NA	NA	NA	NA
2007	1.5 ^d	1.3 ^d	NA	NA	NA	NA
2008	1.5 ^d	1.5 ^d	NA	NA	NA	NA
2009	1.7 ^e	NA	NA	NA	NA	NA

NA: not available; NI: not included.

^a Source: [12].

^b Source: [14].

^c Source: [15].

^d Source: [13].

^e Source: original data from the Unlinked Anonymous Testing Programme in Catalonia.

different trend than, for example, those in the UK [15] where the prevalence was systematically increasing over the years (Table).

HIV prevalence among pregnant women in the World Health Organization European Region [16] has been monitored using three methods: seroprevalence studies based on UAT of either newborns or pregnant women, seroprevalence studies based on multiple data sources (for other sexually transmitted diseases such as syphilis or hepatitis), and systematic collection and reporting of the results of diagnostic testing carried out among pregnant women in antenatal care or at delivery. Most of these countries are nowadays prioritising the third method because of increased accessibility to testing through antenatal care and the establishment of national registers of pregnant women, thus making UAT potentially redundant.

In Catalonia, UAT of neonatal dried blood spots taken for metabolic screening has been carried out since 1994 and the policy of universal antenatal HIV screening was introduced in 1996 [17]. However, to obtain prevalence rates through antenatal HIV screening, we would need information on the number of pregnant women tested for HIV, and in our country the systems to obtain this information are not yet in place. Therefore, UAT has been continued, mainly because data and sample collection are simple, cheap and have the added advantage of providing unbiased prevalence rates. On the other hand, UAT of blood taken from women voluntarily interrupting their pregnancy was stopped in 2007 due to small samples and low representativeness.

As in other regions of Spain, pregnant women in Catalonia are offered HIV screening in the first trimester of pregnancy and, if they are at risk of exposure, also during the third trimester of pregnancy [18]. A survey of HIV testing coverage conducted in Catalonia in the year 2000 found that 89% of women were tested during pregnancy, which at the time was assessed as good coverage [19,20]. Current policy aims at 100% coverage, and there is concern regarding subpopulations that never reach antenatal care because of low educational level, low interest or arrival to the country at the time of delivery. It is worth noting that between the years 2000 and 2009, the foreign population in Catalonia has increased from 2.9% to 15.9% of the total population [21]. Targeted efforts to include foreign mothers are not in place or of dubious efficacy. Strengthening surveillance and promoting testing at voluntary counselling and testing sites may support the already existing and well functioning antenatal care programme. Another important use of the UAT data is to produce estimates of HIV infections in order to plan and monitor the HIV prevention and care programs.

In conclusion, since routine HIV surveillance does not provide data on undiagnosed infections and there is evidence that immigrants may not have access to prenatal care until delivery, data from UAT in Catalonia is

still useful to complement the epidemiological data on this infection. Moreover, UAT among pregnant women is still the best available surrogate for HIV prevalence among the sexually active female population.

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CEEISCAT, Hospital Universitari Germans Trias i Pujol, Badalona (J Masip, A Esteve, JA Rodrigo-Pendàs); Servei de Microbiologia, Hospital Universitari Germans Trias i Pujol, Badalona (V Ausina, L Matas, E Martró, D Sánchez); Unitat de Cribratge Perinatal. LCE. CDB. Corporació Sanitària Clínic, Barcelona (A Maya, M Puliol, F Borja, J M Santos); Direcció General de Salut Pública, Departament de Salut (J L Taberner, R Prats); Servei d'Informació i Estudis, Direcció General de Recursos Sanitaris, Departament de Salut (R Gispert, J J Coll, A Calancha, R Bosser); Clínica d'Ara-Tutor Mèdica (S Barambio, J Fernández, Y Trejo); Clínica E.M.E.C.E. (M Sánchez); Centro Casanova de Ginecología y Planificación, SA (R Novo, M Palma).

Authors' correction

At the request of the authors, the following changes were made on 18 August 2011:

*The sentence that read 'In Italy rates did not change significantly as well as in Scotland [14], in Germany (Berlin) and the UK (London inner city), there was an increasing trend from 0.4 to 0.7 and 1.8 to 2.2, respectively [14].' was replaced by the following: 'In Italy [14,15] rates did not change significantly as well as in Scotland [15] and Germany [15].'

** Numbers and sources in the table were corrected.

*** References were corrected and renumbered in the text and reference list.

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5.2. Article 2

Pilot study to introduce a notification card for partner notification of sexually transmitted infections in Catalonia, Spain, June 2010 to June 2011.

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RESUM

Introducció: Es realitzà un estudi transversal en 10 centres d'atenció primària de Catalunya per determinar l'aplicabilitat, acceptabilitat i rendiment de la notificació a parelles sexuals d'un diagnosticat d'ITS mitjançant l'ús d'una targeta de notificació per part del pacient "patient referral", i per descriure les característiques clíniques i socio-demogràfiques dels casos índex.

Mètodes: Durant un any, els metges que diagnosticaren les ITS de declaració obligatòria van entregar al pacient diagnosticat, tantes targetes com les que aquest manifestava que podria entregar a les seves parelles sexuals. A la vegada, el cas índex emplenava un qüestionari amb informació d'edat, sexe, orientació sexual, nombre de parelles, tipus de relació (ocasional, estable) i raons per les quals no podria entregar la targeta de notificació a les parelles sexuals. Els professionals sanitaris també van emplenar un qüestionari sobre l'acceptabilitat i factibilitat d'entregar la targeta i explicar als casos índex el procediment de la notificació a parelles sexuals. Es va calcular medianes, rangs, intervals de confiança del 95% i desviacions estàndard, de les variables quantitatives. Les proporcions amb interval de confiança del 95% de les variables qualitatives. S'usaren el test xi quadrat i el test exacte de Fisher per l'anàlisi bivariant de les qualitatives i la T d'Student per les quantitatives. Es va utilitzar el paquet estadístic STATA 10.0 (Statacorp, Texas, United States).

Resultats: Es van incloure 219 casos índex (mitjana d'edat: 32,3 anys, DS: 9,3 anys, Rang: 15-57 anys); 130 homes (59%) i 89 dones (41%). Setanta i un dels 130 homes era homosexual (55%). Els homes que tenen sexe amb homes eren d'edat més avançada que els heterosexuals (homes i dones) (4,8 anys en comparació amb 30,9 anys, $p < 0,001$). Les infeccions més freqüents en els casos índex foren: infecció per clamídia (41%, $n=90$), gonorrea (18%, $n=39$); i sífilis (16%, $n=35$). Es van identificar 9 casos d'infecció per VIH (4%). La proporció de dones

amb infecció per clamídia fou superior a la dels homes (53 de 90 comparat amb 20 de 90, $p=0,002$). La proporció d'homes que tenen sexe amb homes infectats per sífilis fou superior que entre els heterossexuals (homes i dones) (29 de 35 comparat amb 5 de 35, $p<0,001$). Pel que fa a la infecció per VIH, 6 de 9 eren homes que tenen sexe amb homes i 3 de 9 homes heterossexuals. Els casos índex reportaren haver tingut 687 parelles sexuals (rang de 1 a 30 parelles, mitjana: 3 parelles per cas índex). Les dones i els homes heterossexuals reportaren una mitjana de 1,7 parelles i els homes que tenen sexe amb homes reportaren una mitjana de 6,2 parelles sexuals ($p<0,001$). Es van entregar 300 targetes de notificació que corresponien a 300 parelles sexuals que rebrien la targeta de les 687 reportades pels casos índex, el que fa un rendiment d'entrega de targeta del 43,7%. La raó principal per no entregar la targeta era que no coneixien com re contactar a les seves parelles (38%). El nombre de persones receptores de la targeta que acudiren a un centre assistencial amb la targeta de notificació fou baix.

Conclusions: l'estratègia de notificació a les parelles per part del pacient, tipus "patient referral", pot assolir un nivell alt de contacte de parelles. Tot i així, el contacte i el lliurament de la targeta no es tradueix inevitablement en una visita al centre assistencial per part de la parella. Les dones heterossexuals foren les que més targetes entregaren per parelles reportades i els homes que tenen sexe amb homes foren els que, malgrat tenir més parelles, van poder entregar molt poques targetes, fonamentalment pel tipus de relació anònima i ocasional. Aquestes troballes indiquen la necessitat de trobar mètodes alternatius de notificació a les parelles difícilment contactables.

Pilot study to introduce a notification card for partner notification of sexually transmitted infections in Catalonia, Spain, June 2010 to June 2011

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We conducted a cross-sectional study in 10 primary care centres in Catalonia, to determine applicability, acceptability and effectiveness of partner notification cards used by patients diagnosed of a sexually transmitted infection (STI) and to characterise these and their sexual partners. Statutorily notifiable STIs included *Chlamydia* infection, gonorrhoea, syphilis, human immunodeficiency virus (HIV) infection or other STIs as deemed necessary by the treating physician. Between June 2010 and June 2011, 219 index cases were enrolled, of whom 130 were men (59.4%), 71 of them men who have sex with men (54.6%). *Chlamydia* infection (41.1%), gonorrhoea (17.8%) and syphilis (16.0%) were the STIs most frequently diagnosed. HIV infection accounted for 4% of cases. A total of 687 sexual partners were reported, and 300 of these were traceable through the notification card (45.7%). Those who did not report traceable contacts were older (mean age: 34 years versus 31 years, $p=0.03$). The main reason for not distributing the card was anonymous sexual intercourse (38%). Patient referral notification cards can reach a high percentage of sexual partners at risk. However, only few notified sexual partners attended participating health centres. Internet-based partner notification may be considered in order to reach those partners not otherwise traceable.

Introduction

Partner notification is the process through which sexual partners of a patient diagnosed with a sexually transmitted infection (STI) are informed that they have been exposed to infection, so they can be assessed, diagnosed and treated [1]. Partner notification is based on the assumption that the transmission chain of STI can be interrupted when both symptomatic and asymptomatic exposed individuals are assessed, diagnosed and treated appropriately [2]. Partner notification for STIs is specifically indicated in cases of *Chlamydia* infection, gonorrhoea, syphilis, or human immunodeficiency virus (HIV) infection [3,4]. Although there is no formal indication or enough evidence to recommend partner notification for other STIs, it may be reasonable in certain circumstances and at the discretion of the treating physician. Clinicians are asked to perform partner notification, but other health professionals such as nurses or social agents can also play a role. Patient referral partner notification seems to be the most cost-effective method compared with other partner notification strategies such as provider referral, conditional referral (where the provider informs the sexual partner(s) in case the patient fails to do so within an agreed period of time) or patient-delivered partner therapy. In a patient referral methodology, only the index case is responsible for notifying their sexual partners of possible infection. The effectiveness of this

process can be increased with the use of a notification card [5,6].

In recent years, Catalonia has experienced a re-emergence of syphilis and HIV infections, the emergence of *Neisseria gonorrhoeae* strains resistant to ceftriaxone [7,8], and outbreaks of Lymphogranuloma venereum [9]. Catalonia has an adult population (15 to 64 years) of almost 5 million [10], and more than 600 new HIV cases were reported in the year 2011 (rate: 8.5/100,000 inhabitants) [11]. Moreover, increased mobility of people, the use of the Internet to find sexual partners (casual and anonymous), and the decreased use of barrier methods are all contributing to the spread of all STI [12-15]. In Spain, no formal guidelines for partner notification have been published yet, nor have there been studies evaluating partner notification. In contrast, 11 of the 24 European Union and European Economic Area (EU/EEA) countries that responded to the survey have regulated partner notification by law [16,17], although only three (Finland, Norway and Sweden) currently observe compulsory partner notification by the health provider and the patient. In Catalonia there has been an increasing interest in implementing partner notification within primary care services since 2007, when gonorrhoea, syphilis, Lymphogranuloma venereum and HIV infection were included as statutorily notifiable infections. The latest version of the STI guidelines published by the Catalan Department of Health strongly recommends partner notification [18], but no standard guidelines or specific support for partner notification have been developed, although there are health centres that have designed their own notification card. For these reasons, a notification card was designed specifically for this study, in order to increase the coverage and efficiency of partner notification as well as to unify and standardise the available tools.

The goal of this study was to facilitate the introduction and standardisation of partner notification for STIs in primary care centres in Catalonia, including the specialist STI unit. We evaluated the applicability (ability of this tool or procedure to be used under real conditions in primary health centres and STI units), and acceptance of this method (willingness and satisfaction of the staff with the use of the tool or procedure to be used under real conditions in primary health centres and STI units), as well as its effectiveness in notifying as many sexual partners of the index case as possible with the support of a notification card. Secondly, we aimed to describe the profile of patients with STIs and their sexual partners.

Methods

Study population

Patients diagnosed with an STI (either clinically or by laboratory test) and attending, during the study period from June 2010 to June 2011, primary care centres (primary health physicians, gynaecologists and midwives)

or the Sexually Transmitted Infection specialist unit (STI unit) were eligible to be enrolled in the study.

Study design

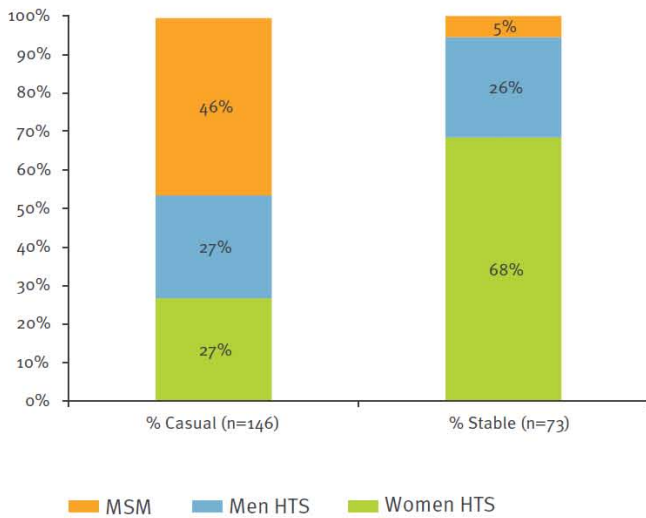
A cross-sectional study was carried out. The study was set up in 10 primary care centres in Catalonia. These centres represented different models of primary STI care (public STI reference units, public and private primary care) and were located in either rural or urban areas. Patients were continuously enrolled during the study period (June 2010 to June 2011). All health professionals participating in the study shared the same standard approaches to STI, defined in the current guidelines for the control and management of STIs in Catalonia [14]. Biological samples were collected from symptomatic patients from the anatomical site of suspicious symptoms, and followed the same laboratory procedures. No further standard criteria were established for additional collection of samples or the screening of asymptomatic partners, e.g. rectal or pharyngeal swabs, these being taken entirely at the discretion of the treating clinician.

Once a laboratory-confirmed STI or suspected (syndromic) case was diagnosed, the index case filled in a specific epidemiological questionnaire. Data collected included: date of index case presenting to the health centre, age, sex, sexual orientation, number of sexual partners during the theoretical infectious period according to clinical guidelines [18], type of relationship (casual or stable), number of partners eligible for being contacted independently of the tool (paper card, SMS, telephone, internet, etc) and of these, the number of partners suitable for notification using the notification card, and reasons why the notification card was not used. Eligible partners were all those that, for each specific infection, had a sexual relationship with the index case within the period of infectiousness, defined by days or months backwards from the date of onset of symptoms in the index case. Eligible partners were classified as: eligible for partner notification using the paper card and those eligible for partner notification using other methods than the card. Partners testing positive were also enrolled as new index cases.

A number of cards equal to the number of partners eligible for being contacted by notification card were distributed to each index case. The health professional received personally the notification card from the notified partner, holding information of date of diagnosis of infection, type of infection, syndromic or laboratory-confirmed, and treatment given to the index case. Syndromic diagnoses were specifically written in a blank space in the notification card: (e.g. urethral syndrome). By counting the notification cards received from notified partners at health centres and recording the date of the partner presenting at the health centre we evaluated the effectiveness of using this notification card.

FIGURE 1

Type of relationship of index cases by sex and sexual orientation, partner notification study, Catalonia, June 2010 to June 2011 (n=219)



HIV: human immunodeficiency virus; HTS: heterosexual; MSM: men who have sex with men.

Index cases stating that it would not be possible for them to trace any of their eligible partners for notification were qualified as non-notifier index cases.

Laboratory results from the index case were included once they were available (including negative results without any alternative diagnosis). For STIs such as HIV infection and syphilis, partner notification did not start until laboratory results were available. A presumptive clinical diagnosis of Lymphogranuloma venereum in men who have sex with men (MSM) triggered a request to subtype *Chlamydia trachomatis*. For other STIs such as *Trichomonas* or herpes simplex infections, causing urethral syndrome or genital herpes, syndromic diagnosis was considered sufficient to start partner notification procedures.

The notification card and the epidemiological questionnaire were piloted by two health professionals with some of their patients for a week prior to their use during the study. This allowed us to adapt both the notification card and the questionnaire, so as to include more understandable words and sentences. Data from patients interviewed during the pilot study were not included in the study.

Data management and analysis

Data collected from the index case's epidemiological questionnaire, from the notification cards and from the questionnaire on acceptability completed by health professionals, were validated and entered into a database designed specifically for the study. Data analysis

was done using STATA 10.0 (Statacorp, Texas, United States). Mean, range, 95% confidence interval (CI) and standard deviation (SD) were calculated for quantitative variables. Proportions and 95% CI for binomial distributions were calculated for qualitative variables. Chi-square and Fisher's exact test were used for bivariate analysis of qualitative variables and Student's T-test for quantitative variables. Men were stratified into two groups: i) MSM, including bisexuals, and ii) heterosexual men. All women were included in a single category. Casual sexual intercourse was defined as an occasional relationship with a partner not considered stable. Relationships lasting more than three months were considered stable. Index cases with negative laboratory results were not excluded from the analysis, having established that there were no socio-demographic differences between index cases with negative and those with positive results. Primary, early latent and secondary syphilis were included in the same category.

Ethical issues

Partner notification is indicated once there is a diagnosis of a statutorily notifiable STI [17]. Informed consent form was therefore not obtained by the health professional. This study was approved by the Ethics Committee of the Hospital Universitari Germans Trias i Pujol. Data in the coordinating centre (Centre for Epidemiological Studies on Sexually Transmitted Infections and HIV/AIDS of Catalonia; CEEISCAT) were treated strictly confidentially following standard procedures. Health professionals participating in the study used their daily practice to contribute to this study.

Results

General description of index cases and distribution of sexually transmitted infections

During the study period, 219 index cases were included (mean age: 32.2 years, SD: 9.3 years, range: 15–57 years), 97 (44%) of whom were recruited in the STI Unit. They were 130 (59%) men and 89 (41%) women. Among men, 71 (55%) were MSM. Most of the MSM were seen at the STI unit (n=63, 89%). MSM were older than heterosexual cases (men and women) (34.8 versus 30.9 years, p=0.001).

Casual relationships were more frequently mentioned by index cases (67%) than stable relationships (33%) (Table 1). Fifty (68%) of the 73 index cases reporting stable relationships were heterosexual women. In contrast, the most frequent sexual orientation among the 146 index cases reporting casual relationships were MSM (46%) (Figure 1). We registered 213 laboratory-confirmed STIs from 239 STI diagnoses (syndromic and laboratory-confirmed), including 20 cases with multiple infections (19 subjects with two infections and one with three infections). A detailed description of the index cases is shown in Table 1. The total number of statutorily notifiable STIs (*Chlamydia* infection, gonorrhoea and syphilis, excluding HIV infection) included in

TABLE 1

Characteristics of the index cases, partner notification study, Catalonia, June 2010 to June 2011 (n=219)

Variable	Number of cases	Percentage of index cases	95% CI
Age (n=219)			
15–25	53	24	18.7–30.1
26–35	98	45	38.0–51.6
36–45	44	20	15.0–26.0
≥45	24	11	7.1–15.9
Sex (n=219)			
Men	130	59	52.5–65.9
Women	89	41	34.0–47.5
Sexual orientation (n=219)			
Heterosexual women	89	41	34.0–47.5
Heterosexual men	59	27	21.2–33.3
MSM	71	32	26.3–39.1
Relationship (n=219)			
Casual	146	67	60.0–72.9
Stable	73	33	27.1–40.0
Laboratory and syndromic diagnosis (n=239 diagnoses)^a			
<i>Chlamydia</i> infection	90	42 ^b	31.4–44.1
Lymphogranuloma venereum	2	2 ^c	0.3–7.8
Gonorrhoea	39	18 ^b	11.9–21.6
HIV infection	9	4 ^b	1.7–7.0
Syphilis	35	16 ^b	10.4–19.8
Primary syphilis	14	40 ^c	23.9–57.9
Secondary syphilis	10	29 ^c	14.6–46.3
Early latent syphilis	4	11 ^c	3.2–26.7
Latent syphilis	7	20 ^c	8.4–36.9
Other laboratory-positive and syndromic STI ^d	40	19 ^b	12.2–22.1
Laboratory-positive and syndromic STI	213	89 ^e	84.4–92.7
Laboratory-negative	26	11 ^e	7.2–15.5
Number of sexual partners mentioned by index case (n=687 partners)			
0–1	103	47	40.3–53.9
2–3	65	30	23.7–36.2
≥3	51	23	17.9–29.5
Notification card distributed by index case (n=300 cards)			
0	48	22	16.6–28.0
1–3	161	73	67.1–79.2
≥3	10	5	2.2–8.2
Reason for not using the notification card (n=99 index cases)^f			
Anonymous sexual partner	43	38	27.5–45.4
Sexual partner lives far	34	30	21.8–39.4
It is not necessary to notify	8	7	3.1–13.5
Other	28	25	17.1–33.8

CI: confidence interval; HIV: human immunodeficiency virus; MSM: men having sex with men; STI: sexually transmitted infection.

^a Includes 19 patients with two infections (*Neisseria gonorrhoeae*+*Chlamydia trachomatis*, n=7; *C. trachomatis*+*Trichomonas vaginalis*, n=2; *C. trachomatis*+*Ureaplasma urealyticum*, n=1; *C. trachomatis*+*Treponema pallidum*, n=2; *N. gonorrhoeae*+*T. pallidum*, n=1; HIV+*C. trachomatis*, n=1; HIV+*T. pallidum*, n=2; HIV+*T. vaginalis*, n=2; *U. urealyticum*+*Mycoplasma genitalium*, n=1) and one patient with three infections (*C. trachomatis*+*N. gonorrhoeae*+*U. urealyticum*).

^b Percentage of the type of infection over all laboratory-positive and syndromic STI (n=213).

^c Percentage of cases within each category.

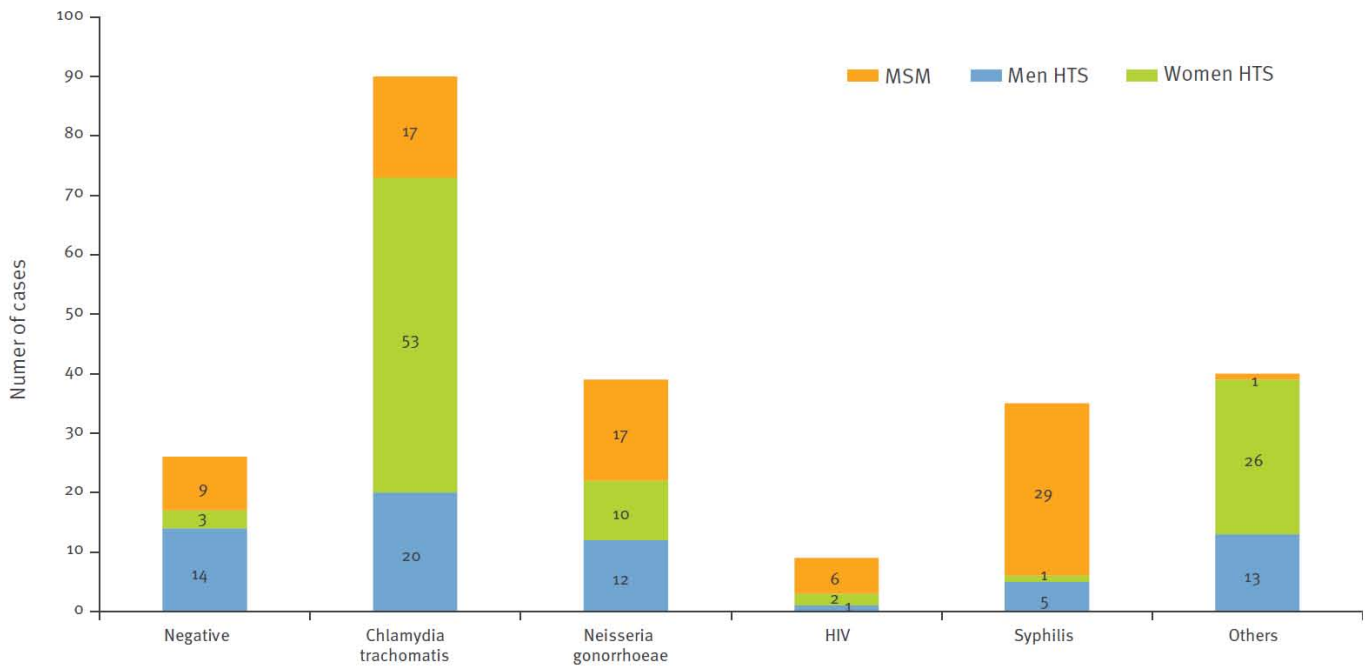
^d *T. vaginalis* (n=20), Human papillomavirus (n=6), Hepatitis B virus (n=4), *U. urealyticum* (n=4), *M. genitalium* (n=3), Herpes simplex (n=3).

^e Percentage of results over all laboratory and syndromic diagnoses (n=239).

^f This question accepted more than one answer.

FIGURE 2

Distribution of sexually transmitted infections by sex and sexual orientation, partner notification study, Catalonia, June 2010 to June 2011 (n=219)^a



HIV: human immunodeficiency virus; HTS: heterosexual; MSM: men who have sex with men.

^a The 219 cases had a total of 239 diagnoses and included 19 patients with two infections (*Neisseria gonorrhoeae*+*Chlamydia trachomatis*, n=7; *C. trachomatis*+*Trichomonas vaginalis*, n=2; *C. trachomatis*+*Ureaplasma urealyticum*, n=1; *C. trachomatis*+*Treponema pallidum*, n=2; *N. gonorrhoeae*+*Treponema pallidum*, n=1; HIV+*C. trachomatis*, n=1; HIV+*Treponema pallidum*, n=2; HIV+*T. vaginalis*, n=2; *U. urealyticum*+*Mycoplasma genitalium*, n=1) and one patient with three infections (*C. trachomatis*+*N. gonorrhoeae*+*U. urealyticum*).

the study was 164 representing 15% of all STIs declared in Catalonia during the study period (n=1,158).

The most frequent STIs were: *Chlamydia* infection, including two cases of Lymphogranuloma venereum, (41%, n=90), gonorrhoea (18%, n=39) and syphilis (16%, n=35). HIV infection accounted for 4% (n=9) and all were newly diagnosed HIV infections. Other STIs represented 18% (n=40) of the sample. Twenty-six patients had negative laboratory results and their diagnosis was therefore exclusively clinical and syndromic (12%).

Figure 2 shows the number of STIs by diagnosis, sex and sexual orientation. The proportion of women among *Chlamydia*-infected patients was higher than that of heterosexual men (53 of 90 versus 20 of 90, p=0.002). Syphilis was proportionally more frequent among MSM than heterosexual men (29 of 35 versus 5 of 35 p<0.001). Most HIV infections were in MSM compared with the heterosexual population (6 of 9 versus 3 of 9, p=0.03). Both cases of Lymphogranuloma venereum were diagnosed in MSM.

Number of sexual partners and cards distributed and recovered

Overall, the index cases reported having had 687 sexual partners during the infectious period (range: 1–30, mean: 3 partners per index case). Female index cases reported a mean of 1.7 sexual partners, heterosexual men of 1.7, and MSM of 6.2 (p<0.001).

A total of 300 notification cards were reported to be distributed by the index cases to their sexual partners (corresponding to 300 sexual contacts eligible to be contacted using the notification card). The remaining 387 partners were those eligible to be notified by other means than partner notification paper card, including those that may be impossible to trace by the index case. There were 59 notification cards distributed to heterosexual men, who reported a total of 100 sexual partners (ratio of cards distributed/contacts reported: 0.59, 95%CI: 0.48–0.68). There were 108 notification cards distributed to women who reported a total of 144 sexual partners (ratio: 0.75, 95% CI: 0.62–0.79) and 133 to MSM who reported 443 sexual partners (ratio: 0.30, 95% CI: 0.26–0.35).

TABLE 2

Characteristics of non-notifier^a group of index cases, partner notification study, Catalonia, June 2010 to June 2011 (n=48)

Variable	Number	Percentage ^b	p value ^c
Sexual orientation (n=48)			
Heterosexual women	10	11	0.003 ^d
Heterosexual men	20	34	
MSM	18	25	
Relationship (n=48)			
Casual	37	25	0.08 ^d
Stable	11	15	
Age (n=48)			
15–25	7	13	0.17 ^d
26–35	21	21	
36–45	12	27	
>45	8	33	
Number of sexual partners referred (n=48)			
0–1	29	28	0.08 ^d
2–3	9	14	
>3	10	20	
Laboratory diagnosis (n=55) ^e			
<i>Chlamydia</i> infection	16	18	0.2
Gonorrhoea	9	23	0.8
HIV	3	33	0.4
Syphilis	9	26	0.6
Other STI	8	20	0.8
Negative	10	38	0.03

HIV: human immunodeficiency virus; MSM: men having sex with men; STI: sexually transmitted infection.

^a Non-notifier index cases are those stating that it would not be possible for them to trace any of their eligible partners for notification either using a notification paper card or by other means.

^b The denominator was the total of individuals included in the respective groups as presented in Table 1 (e.g. 10 non-notifier HTS women among 89 HTS persons included in the study).

^c The baselines are considered as the group of notifiers.

^d P test for trend.

^e The number of laboratory results (n=55) exceeds the number of non-notifier index cases because some of them had more than one STI.

The ratio of cards distributed/contacts reported was lowest among MSM, followed by heterosexual men and heterosexual women (p test for trend=0.003). Overall, thirty-one cards were returned to participating health centres (10%) and the card holders were assessed by health professionals and treated as necessary following diagnosis. This percentage was higher in the STI Unit (20%, p=0.003). The main reason for not using a notification card was that sexual contact was

anonymous 38%. Those partners that were notified by index cases but did not deliver a notification card or mention it on arrival at the health centre were not registered as contacts and were only enrolled as index cases.

Non-notifier index cases

Of the 219 index cases enrolled in the study, 99 (45%) stated that it would be impossible to use the notification card at least for one of their partners. Among them were 48 (48%) for whom it was impossible to notify any of their partners (non-notifiers). These non-notifier index cases were older than other index cases (34 versus 31 years, p=0.03), independently of sexual orientation. In Table 2 we show a detailed description of non-notifier index cases.

Discussion

This is the first study evaluating partner notification for STIs in Catalonia or Spain. Most of our findings are in line with recently published studies in the United States (US) and Switzerland [19,20], which reported higher-risk behaviour by MSM (greater number of sexual partners, including casual and anonymous sexual intercourse), and a higher proportion of syphilis among MSM and *Chlamydia* infection among women.

It is of note that female index cases indicated that they were able to give the card to their sexual partners more often than heterosexual men (ratio 0.75 versus 0.59). This can be explained by socio-cultural perceptions, or more probably, by the type of relation maintained with sexual partners (more frequently stable). We suspect that women were more frequently infected by their stable partner than other groups.

One finding of our study is the relatively low yield of partner notification cards distributed and recovered (patients returned). However, we consider this number as an underestimation. This study was not designed for collecting returned cards, although a certain number were collected by the participating centres. Given that there are hundreds of primary care and private centres in Catalonia that can see individuals with suspected STIs, the study was unable to include all these centres, and could thus only focus on a limited and representative number of centres. Moreover, a certain number of contacts may have visited a health centre without presenting the card (uncontrolled).

We also suspect that a lack of awareness and lack of concern about asymptomatic sexually transmitted infections may be one of the explanations for the low proportion of sexual partners presenting to health centres after being notified by the index case.

It is important to mention that a larger proportion of cards were retrieved in the STI unit compared with the rest of the participating centres (not specialised, 20%). This relatively high percentage may be attributable to the specialised attention given to patients in the STI

unit and the higher probability of effectively assessing and treating sexual partners of index case seen in this unit.

The main finding of our study with respect to partner traceability is that close to half of all sexual partners were traceable through a notification card distributed by the index cases (n=300 of 687, 44%) but it is also important to note the high number of partners that could not be contacted due to anonymous and casual sexual intercourse.

Consequently, additional notification strategies should be implemented to reach a higher proportion of exposed contacts and to overcome communication barriers. One of the strategies is email or website notification using pseudonyms. The use of the internet is becoming highly popular for sexual partner research, especially among high-risk groups. The use of email and specially designed websites under the control of health authorities can guarantee confidentiality and quality of the information given to sexual partners exposed. In fact, this may be the only way to contact a majority of sexual partners [21-24]. Some clinics in the US and Australia are already using this technology with promising results [25,26]. However, most of the literature about partner notification for STI was carried out in other countries with different socio-cultural contexts such as Australia, Canada, the US, Guatemala and Kenya. We cannot ascertain the real impact of this strategy (number of sexual partners finally screened in health services), and we relied on the previous studies that evaluated these indicators [2,6,27,28]

Since this study was done under real conditions in each health centre, a standard protocol to test sexual partners was not used in our study. Therefore, the testing of sexual partners may have been addressed differently by the participating centres. Comprehensive routine or sexual practice-based screening of different anatomical sites (rectal and pharyngeal swabs in the case of anal or oral intercourse) was not standard procedure. Although sexual partners attending health centres with a notification card were assessed according to their sexual orientation, sexual practice and symptoms, we cannot ensure that comprehensive testing was done by all participating centres in all sexual partners, independently of the presence of symptoms. In Catalonia, despite current guidelines recommending partner notification, there is still no clear partner notification strategy, a gap which needs to be closed. Considering the high proportion of asymptomatic STIs, comprehensive screening of sexual partners, irrespective of the presence of symptoms, should be offered by all health professionals treating STIs, in order to optimise partner notification practices and improve their effectiveness.

In conclusion, partner notification through the use of a notification card is a feasible (applicable and acceptable) strategy in Catalonia given its high

acceptability among healthcare workers and index cases. Nevertheless, there are some variations in the use of the notification paper card, MSM being the ones with more difficulties to use it due to the highest number of anonymous sexual contacts. Moreover, the capacity of the card to bring contacts to the healthcare system is very sensitive to the awareness of health professionals and the site where they are working (STI unit, Care Programme for Sexual and Reproductive Health or primary healthcare physician), and also depends on whether the population knows about the services provided by each centre. Therefore, there is room for improvement in the healthcare system derivation procedures.

In addition, further strategies should be developed and implemented to maximise the impact of partner notification strategies, such as web-based notification for anonymous contacts using pseudonymous name. Finally, there is a need for a clear partner notification strategy including guidelines on testing procedures according to sexual orientation and sexual practice, and independently of the presence of symptoms.

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5.3. Article 3

Twenty years trends and socio-demographic characteristics of HIV prevalence in women giving birth in Catalonia, Spain, 1994 to 2013.

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RESUM

Introducció: Els estudis de prevalença en poblacions sentinella constitueixen una de les estratègies clau per al seguiment de l'epidèmia del VIH. L'objectiu fou estudiar l'evolució i tendències temporals de prevalença del VIH a la dona embarassada en funció de les seves característiques socio-demogràfiques, més especialment en funció del país d'origen de la mare i lloc de residència a Catalunya.

Mètodes: Es recolliren mostres per la detecció d'anticossos anti-VIH a partir del Programa de Detecció Neonatal de metabolopaties que té una cobertura del 99% dels nadons vius a Catalunya. El càlcul de la grandària fixà una mostra del 50% de tots els nadons vius. Aquestes mostres, es recullen cada dos mesos, per tal de corregir possibles biaixos de temporalitat. Dues mostres de sang foren recollides en paper secant (Scheilcher and Schuell no.903TM, Dassel, Germany) i emmagatzemades a 4°C de temperatura fins a la seva utilització. Els anticossos foren determinats utilitzant el test d'aglutinació modificat Serodia IgG (GACPAT) per VIH-1 (Fujirebio Diagnostics). La re confirmació de les mostres positives fou realitzada a l'Hospital Universitari Germans Trias i Pujol utilitzant el mètode ELISA per VIH-1 i VIH-2. La prevalença anual es calculà considerant el nombre de mostres positives del nombre total de mostres analitzades, amb un interval de confiança del 95%. El test de Cochran-Armitage fou utilitzat per a l'estudi de tendències de les proporcions amb un nivell de significació de 0,05. El xi-quadrat i el test exacte de Fisher foren utilitzats per a les comparacions estadístiques de prevalença entre països o bé regions de naixement de la mare. Per a l'anàlisi estadística es va utilitzar SAS v 9.3.

Resultats: L'evolució del nombre de nascuts vius ha anat augmentant tant de mares autòctones com estrangeres, fins a l'any 2008 quan canvià la tendència, per disminuir notablement el nombre de nascuts vius. Entre 2010 i 2013, el nombre de nascuts vius disminueix en un 5,9% en mares estrangeres i un 1,7% en autòctones. En el període de 20 anys s'han analitzat per detectar anticossos anti-VIH un total de 624.912 mostres de sang seca de nadons. Les taxes de prevalença de VIH disminueixen entre 1994 i 2007, de 0,32% (IC 95%:

0,25-0,40) a 0,15% (IC 95%: 0,12-0,20), i a partir de 2008 la tendència no varia. A Barcelona ciutat la tendència és a disminuir ($p < 0,05$) de 0,43% (IC 95%: 0,27-0,64) a 0,23% (IC 95%: 0,14-0,37). També va disminuir a les ciutats de més de 200.000 habitants ($p < 0,005$) de 0,43% (IC 95%: 0,23-0,73) a 0,20% (IC 95%: 0,10-0,36) i en ciutats de ≤ 200.000 habitants ($p < 0,0001$) de 0,25% (IC 95%: 0,18-0,35) a 0,13% (IC95%: 0,09-0,17). Pel que fa a l'estudi segons lloc de naixement de la mare, es disposa d'informació dels anys 2007 a 2013. En aquest període les dones estrangeres que donen a llum mostren prevalença de VIH superior (0,26%) a les autòctones (0,10%). Entre les estrangeres, la prevalença és superior en les procedents de l'Àfrica Sub-Sahariana (0,40%) i les de l'Amèrica Llatina (0,20%). Segons ciutat de residència, els nivells més alts de prevalença (0,28%) es troben en dones estrangeres residents a ciutats de ≤ 200.000 habitants. Mentre que els més baixos (0,09%) es troben en dones autòctones residents també, a ciutats de ≤ 200.000 habitants. Quan ho analitzem per país o regió d'origen, són les dones procedents de l'Àfrica Sub-Sahariana i que viuen a Barcelona ciutat les que mostren els nivells més alts de prevalença (0,59%) ($p < 0,001$) seguit de les Sub-Saharianes que viuen a ciutats de ≤ 200.000 habitants (0,40%) ($p < 0,0001$) i de les Llatinoamericanes que viuen a Barcelona Ciutat (0,29%) ($p < 0,001$)

Conclusions: Tot i la baixa prevalença de VIH en la dona embarassada a Catalunya (0,12% a l'any 2013), el fet de que les poblacions estrangeres procedents d'àrees endèmiques presentin una afectació desproporcionada pel que fa a aquesta infecció, justifica dedicar especial atenció a l'estudi de la prevalença del VIH a la dona embarassada. A partir de 2008, les taxes més altes de prevalença es troben en dones de l'Àfrica Sub-Sahariana o bé Amèrica Llatina, que viuen a Barcelona ciutat o bé en ciutats ~~de~~ ≤ 200.000 habitants. Aquesta realitat indica que els programes de pre i post natal haurien de ser reforçats i mantinguts per tal de garantir l'abordatge a temps i amb qualitat de les dones infectades pel VIH, tenint en compte les realitats culturals i salvant les possibles barreres de llenguatge.

Twenty years trends and socio-demographic characteristics of HIV prevalence in women giving birth in Catalonia (Spain)

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ABSTRACT

Background: Studies of the prevalence of HIV in sentinel populations are one of the key strategies to monitor the HIV epidemic. We describe HIV prevalence trends and identify differences across time in the sociodemographic characteristics of HIV-infected women giving birth in Catalonia.

Methods: We used dried blood specimens, residual to newborn screening, which have been collected in Catalonia every 2 months since 1994. The total number of samples obtained until 2009 and in 2013 represented half of yearly newborns. From 2010 to 2012, the total number of samples obtained represented a quarter of yearly newborns. We studied the prevalence by year and place of current residence (Barcelona-city, cities >200,000 inhabitants and cities ≤ 200,000 inhabitants) and by the mother's birth country. A total of 624,912 infants were tested for HIV antibodies from January 1994 to December 2013.

Results: HIV prevalence trends among women giving birth in Catalonia decreased until 2007. Thereafter, there was a change to a steady trend until 2013. However, among foreign women giving birth and living in cities ≤ 200,000 inhabitants, the prevalence of HIV increased from 2007 to 2013.

Conclusion: To ensure early identification and treatment of HIV-infected mothers, it is essential to maintain HIV surveillance programs and pre- and post-natal screening programs, both in Barcelona and in cities with 200,000 inhabitants or less, especially in immigrant women.

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Veinte años de seguimiento de la prevalencia del VIH y características sociodemográficas en mujeres que dan a luz en Cataluña (España)

RESUMEN

Antecedentes: Los estudios de prevalencia del VIH en poblaciones centinela son una de las estrategias clave para monitorizar la epidemia. Describimos tendencias de la prevalencia de VIH e identificamos diferencias en el tiempo y según las características socio-demográficas de las mujeres que dan a luz infectadas por el VIH en Cataluña.

Métodos: Utilizamos muestras de sangre seca, residuales al cribado de recién nacidos que se recoge cada dos meses desde el año 1994. El total de muestras obtenidas hasta el 2009 y en 2013, representa la mitad de los recién nacidos anuales. En los años 2010 a 2012, el total de muestras obtenidas representa un cuarto de los recién nacidos anuales. Estudiamos la prevalencia por año y lugar de residencia (Barcelona-ciudad, ciudades de más de 200.000 habitantes y otras ciudades o pueblos de ≤ a 200.000 habitantes) y por lugar de nacimiento de la madre. Entre enero 1994 y diciembre 2013, fueron cribados de existencia de anticuerpos anti-VIH 624.912 recién nacidos.

Resultados: La prevalencia de VIH en las mujeres que dan a luz en Cataluña decrece hasta el año 2007, estabilizándose en 2013. Sin embargo, entre las extranjeras que dieron a luz y que viven en ciudades de ≤ a 200.000 habitantes la prevalencia de VIH aumenta entre 2007 y 2013.

Conclusión: Es fundamental mantener la vigilancia del VIH y los programas pre y post natal en Barcelona ciudad y ciudades de ≤ a 200.000 habitantes, y especialmente en las mujeres extranjeras para asegurar un temprano abordaje de las infectadas por el VIH.

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Palabras clave:

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Introduction

Studies in sentinel populations to estimate HIV prevalence are the key strategies to monitor the epidemic¹. Pregnant women are an important group to target for HIV prevention as early diagnosis and appropriate management reduces mother to child transmission. Monitoring HIV prevalence in this group has been done using different methods such as back projection from reported cases of AIDS due to perinatally acquired HIV infection² or unlinked anonymous surveillance³⁻⁷ or testing programs in antenatal care or abortion clinics⁸.

In Catalonia, estimations of pregnant women's HIV prevalence cannot be done from information collected in antenatal care or abortion clinics because the standard HIV surveillance questionnaire doesn't ask about pregnancy status. Unlinked anonymous testing was introduced in the Integrated Surveillance System of HIV/AIDS/STI of the Health Department (Generalitat de Catalunya) in 1994, as a way to monitorize HIV prevalence with the minimum participation bias, in key populations. Originally, Intravenous Drug Users, Men who have Sex with Men and Female Sex Workers were chosen as high risk populations. Since the offering of an HIV test to all pregnant women was mandatory in the local protocol, and since a newborn metabolic screening program was in place with a very high coverage (99%), newborns were also included as a sentinel population to estimate HIV prevalence among pregnant women. The unlinked anonymous newborn survey has provided information on HIV prevalence by area of residence since 1994 and by country of origin since 2007 and now includes approximately 50% of live births in Catalonia. The survey includes women whose HIV infection has already been diagnosed as well as those unaware of their infection, giving a measure of overall HIV prevalence in pregnant women.

The increase of immigration occurred in Spain and Catalonia within the last 20 years with a steady trend of migrants since the year 2009. The pattern of migration of women 15 to 64 years old is similar, both in big and small cities, increasing up to 2009 and stable after then. Percentages of migrant women are the highest in Barcelona, followed by 4 cities > 200,000 (Badalona, Hospitalet de Llobregat, Terrassa and Sabadell) and cities ≤ 200,000 inhabitants.

According to these data, it is meaningful to study the HIV prevalence by mother's country of birth and place of current residence. Other researchers have studied serological markers of HIV and other infections in Spain^{9,10}. The study of the geographic distribution of HIV prevalence in women giving birth may be an additional tool to help targeting geographic areas for intervention. Although ecological studies are not conclusive¹¹, taking profit of data already available helps reducing costs and better targeting for further studies. The aim of this study was to describe HIV prevalence trends in women giving birth and identify differences on their socio-demographic characteristics by place of current residence in Catalonia during a 20 years period (1994 to 2013) as well as describe the potential role of immigration more specifically for the period 2007 to 2013.

Methods

Collection of samples

The neonatal dried blood spot survey, residual to newborn screening¹², takes left over dried blood spots taken from newborn 3 days after birth and tests them for maternal HIV infection. These blood specimens are being collected, in order to avoid seasonality, every two months. The obtained sample size represents half of the

yearly newborns up to the year 2009 and also for the year 2013. Samples from 2009 to 2012 represent only a quarter of the yearly new born¹³ in Catalonia. All samples are irreversibly unlinked and anonymized prior to HIV testing. Anonymity was guaranteed by using a computer-aided coding process at the Neonatal Early Detection Program therefore, the results of HIV antibody testing can't be linked with any patient identification number. Regional distribution of yearly samples within Catalonia is proportional to regional birth rate.

Variables

Variables collected in the study were: HIV results from testing new born as a surrogate of HIV status of the mother (100% completion), age (100% completion), mother's country or region of birth (from 2007) (>95% completion) and mother's place of current residence (99.6% completion). In order to allow comparisons we established three categories of mother's place of current residence: Barcelona city, cities >200,000 (Hospitalet de Llobregat, Terrassa, Sabadell and Badalona) and cities or towns ≤ 200,000 inhabitants.

Mother's country or region of birth was grouped into Latin America, Sub-Saharan Africa, Spain and rest of the world.

As background information, population data by country of birth were collected from the Annual statistical report of Catalonia. Catalan Institute of Statistics¹³ and classified according to populations' origin (Spanish and foreign born) and grouped by categories used to study mother's place of current residence: Barcelona city (more than 1.5 million inhabitants), cities > 200,000 and cities or towns ≤ 200,000 inhabitants.

Laboratory methods

Two drops of blood were collected on filter paper discs (Schleicher and Schuell no. 903TM, Dassel, Germany) and stored at 4°C until used. HIV antibodies were determined using a modified Serodia IgG antibody-capture particle agglutination test for HIV-1 (Fujirebio Diagnostics)¹⁴. Positive samples were sent to the Microbiological Service of the University Hospital Germans Trias i Pujol to confirm the results using an IgG antibody capture ELISA for HIV-1 and HIV-2. Until 2001 this was done using the GACELISA test (Murex, UK)¹⁵. In 2002 up to 2006, this confirmatory test was replaced with the Pasteur HIV-1/2 GenElavia Mixt ELISA (BioRad, Spain) after checking that normal and external valid values were similar for both tests¹⁶. From 2007 to 2009, the test used was BED-CEIA Assay (Calypte Biomedical Inc, Portland, OR, USA) and from 2010 until nowadays, Vitros HIV1 +2 Reagent (Ortho Clinical Diagnostics Inc, Cardiff, Wales, UK) is the test used. The surveys are conducted in collaboration with the Catalan Neonatal Early Detection Programme, Service of Biochemistry and Molecular Genetics, Hospital Clinic, Faculty of Medicine, Barcelona, Spain, as well as with the Microbiology Laboratory of the Hospital Germans Trias i Pujol, where reactive samples are confirmed.

Statistical analysis

The annual HIV prevalence among women giving birth was computed as the number of HIV-positive samples divided by the total number of HIV-positive and HIV-negative samples tested each year. Confidence intervals for proportions were calculated by using the Clopper and Pearson method. The Cochran-Armitage test was used as a test for trends of proportions with a 0.05 significance level. Statistical comparisons of prevalence between country or region of birth were performed using chi-squared analysis and Fisher's exact test.

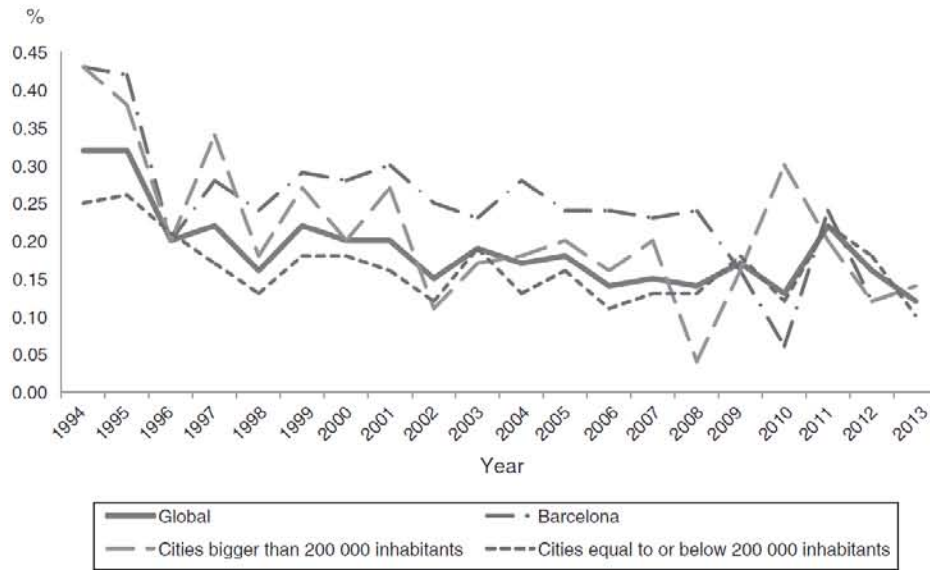


Figure 1. Trends in HIV prevalence (%) among women giving birth in Catalonia, 1994–2013.

A total of 624,912 infants were tested for HIV antibodies during the 20 years studied (1994–2013). We present the evolution of the population of women aged 15 to 64 years provided that the age range of women giving birth from whom blood samples were taken was 10 to 56 years old. The annual number of live births is also presented to help the interpretation of HIV prevalence.

Due to reductions in financial support, the number of HIV tests performed was reduced during the period 2008 to 2012, although the distribution of samples tested by the mother's place of current residence has been maintained overtime.

Data were analyzed using SAS v 9.3

Results

During the twenty years of study, the number of live births in Catalonia has been rising up to 89,327 in the year 2008¹⁷ and thereafter decreasing to 71,771 in 2013^{18,19}. In both, Spanish and foreign born mothers, the number of live births increased up to the year 2008 and decreased mainly in Spanish mothers^{18,19} up to 2010. From 2010 until 2013, there was a 5.9% and 1.7% reduction of foreign and autochthonous live births, respectively. Median age of mothers is 31 years (interquartile range: 28 to 34) being foreign mothers, slightly younger than autochthonous and no differences were found by mother's place of current residence.

Despite changes in population numbers overtime, there were no variations across the geographical categories of cities established by our study.

During 1994 to 2007, HIV prevalence trends among women giving birth in all Catalonia are decreasing from 0.32% (95%CI:0.25–0.40) to 0.15% (95%CI:0.12–0.20) ($p < 0.0001$) (Figure 1). In Barcelona city trends are decreasing ($p < 0.05$) from

0.43% (95%CI:0.27–0.64) to 0.23% (95%CI:0.14–0.37) as well as in cities > 200,000 inhabitants ($p < 0.005$), from 0.43% (95%CI:0.23–0.73) to 0.20% (95%CI:0.10–0.36) and in cities \leq 200,000 inhabitants ($p < 0.0001$), from 0.25% (95%CI:0.18–0.35) to 0.13% (95%CI:0.09–0.17), but from 2008 onwards the trend is steady in each geographical category.

In summary, for all the 20 years' period, HIV prevalence of all women giving birth is higher in Barcelona city than the rest of the Catalan cities (Table 1).

Information about country of birth was only available from 2007 to 2013. During this period the number of women aged 15 to 64 years living in Catalonia increased by 2% as well as the number of foreign women of this age group.

In the city of Barcelona and other cities > 200,000 inhabitants, the number of women aged 15 to 64 years decreased slightly, by 0.2% and 0.3%, respectively. While it increased by 4% in cities \leq 200,000 inhabitants. The percentage of foreign women over the total number of women of this age group increased everywhere, by 2% in Barcelona city and by 3% in the other two categories of cities (> and \leq to 200,000 inhabitants).

Over the years 2007–2013, foreign women giving birth and living in any of the geographical categories of cities established in our study, showed higher HIV prevalence (0.26%) than Spanish women (0.10%). The highest (0.28%) and lowest (0.09%) levels of HIV prevalence were found in cities \leq 200,000 inhabitants among foreign and Spanish women giving birth, respectively (Table 2).

In all Catalonia, the 7 years period HIV prevalence was higher among women born in Sub-Saharan Africa (0.40%) followed by Latin Americans (0.20%) (Table 3).

When looking at the current place of residence, the highest HIV prevalence was found in women from Sub-Saharan Africa (0.59%) ($p < 0.001$) and living in Barcelona city or in cities \leq 200,000

Table 1
HIV prevalence in women giving birth in Catalonia, by place of current residence. 1994–2013.

Place of current residence	HIV +	N test	HIV prevalence %	95%CI
Barcelona city	312	123177	0,25	0,23–0,28
Cities >200,000 inhabitants	162	79864	0,20	0,17–0,24
Cities \leq 200,000 inhabitants	654	397842	0,16	0,15–0,17

Table 2

HIV prevalence in women giving birth in Catalonia, by country of birth and place of current residence, 2007-2013.

Country of birth	Foreign born			Spanish born			P values
	Place of current residence	N test	HIV + HIV prevalence % (95%CI)	N test	HIV + HIV prevalence % (95%CI)	HIV prevalence % (95%CI)	
Barcelona city	10682	25	0.23 (0.15-0.35)	23037	33	0.14 (0.10-0.20)	0.06
Cities >200,000 inhabitants	7642	13	0.17 (0.09-0.29)	16110	22	0.14 (0.09-0.21)	0.529
Cities ≤ 200,000 inhabitants	34184	96	0.28 (0.23-0.34)	94109	83	0.09 (0.07-0.11)	<0.001

Table 3

HIV prevalence in women giving birth in Catalonia, by country or region of birth, 2007-2013.

Country or region of birth	Test N	HIV +	HIV Prevalence % (95%CI)
Spain	133256	138	0.10 (0.09-0.12)
Northern & Sub-Saharan Africa [*]	20641	82	0.40 (0.32-0.49)
Latin America ^{**}	15827	31	0.20 (0.13-0.28)
Rest of the world	16040	21	0.13 (0.08-0.20)

^{*} Countries of Northern & Sub-Saharan Africa in this study are the following: Morocco, Algeria, Tunisia, Burkina Faso, Cameroon, The Gambia, Equatorial Guinea, Ghana, Mali, Mauritania, Mozambique, Niger, Nigeria, Senegal and Sudan

^{**} Countries of Latin America in this study are the following: Argentina, Bolivia, Brazil, Chile, Colombia, Cuba, Dominican Republic, Ecuador, Panama, Paraguay, Peru and Uruguay.

inhabitants, (0.40%), ($p < 0.0001$) followed by those from Latin America and living in Barcelona city (0.29%) ($p < 0.001$) (Table 4).

Discussion

HIV prevalence among women giving birth in Catalonia is currently low (0.12% in 2013), although a significant difference was found on comparing Spanish and foreign born women from HIV endemic areas. As stated by a recent ECDC report ²⁰, between 2007 and 2011 migrant populations in Europe are disproportionately affected by HIV, although there might be significant variations between countries.

We may hypothesize that due to the economical crisis starting in 2008, economically and socially deprived populations (foreign and autochthonous) living in big cities may have moved to smaller cities where living conditions are easier and less expensive, consequently increasing the social needs in these areas.

Also, to be considered is the reduction of the number of births in Catalonia, starting in 2009, from 89,327 new born in 2008 to 81,137 in 2011. Major reductions are among births in the foreign population: from the year 2010 to 2011 there was a 5.9% and 1.7% reduction of, foreign and autochthonous births, respectively. Nevertheless, these reductions don't seem to affect the HIV prevalence estimations.

In any case, the fact that highest HIV prevalence is found among Sub-Saharan Africa and Latin-America women giving birth and living in Barcelona or in towns and cities ≤ 200,000 inhabitants, indicates that HIV surveillance, antenatal and mother's care have

to be maintained and enhanced in both Catalan geographical areas, with special attention to address cultural and language barriers, in order to ensure proper identification and timely treatment of HIV infected mothers.

In Catalonia, differently to UK ²¹, it is unknown whether foreign born citizens living with HIV are less likely to access healthcare, mainly due to social isolation or insecure immigration status ²². This situation, although improbable because of the universal access to healthcare, may impact on diagnosis and access to HIV treatment. The number of HIV infected women reported as pregnant can only be estimated from unlinked anonymous testing and there is no institutionally established surveillance system to monitor mother to child transmission although data are annually retrieved from a clinicians' managed data base of a cohort of mother and child pairs.

This study has some limitations such as: birth rates by mother's country of birth (foreign and autochthonous) and place of current residence could not be retrieved. Had this information been available it would have helped to better explain our findings.

More accurate estimates of HIV prevalence at district level and not only at town or city level may allow better targeting of resources in bigger cities. This information was not available from the data collected until nowadays, although some changes have been proposed from the year 2014 onwards.

In conclusion, this study reports on the only Catalan population-based HIV prevalence data currently available for women giving birth that has been carried out for two decades; these data have been a valuable tool for monitoring trends, targeting resources and evaluating programs and policies.

Table 4

HIV prevalence in women giving birth in Catalonia by country or region of birth and place of current residence, 2007-2013.

Country or region of birth	Spain			Sub-Saharan Africa [*]			Latin America ^{**}			Rest of the world		
	Place of current residence	Test N	HIV + HIV Prevalence % (95%CI)	Test N	HIV + HIV Prevalence % (95%CI)	Test N	HIV + HIV Prevalence % (95%CI)	Test N	HIV + HIV Prevalence % (95%CI)	Test N	HIV + HIV Prevalence % (95%CI)	
Barcelona city	23037	33	0.14 (0.10-0.20)	1362	8	0.59 (0.25-1.15)	4410	13	0.29 (0.16-0.50)	4910	4	0.08 (0.02-0.21)
Cities >200,000 inhabitants	16110	22	0.14 (0.09-0.21)	2691	8	0.03 (0.01-0.58)	3274	3	0.09 (0.02-0.27)	1677	2	0.12 (0.01-0.43)
Cities ≤ 200,000 inhabitants	94109	83	0.09 (0.07-0.11)	16588	66	0.40 (0.31-0.51)	8143	15	0.18 (0.10-0.30)	9453	15	0.16 (0.09-0.26)

^{*} Countries of Northern & Sub-Saharan Africa in this study are the following: Morocco, Algeria, Tunisia, Burkina Faso, Cameroon, The Gambia, Equatorial Guinea, Ghana, Mali, Mauritania, Mozambique, Niger, Nigeria, Senegal and Sudan.

^{**} Countries of Latin America in this study are the following: Argentina, Bolivia, Brazil, Chile, Colombia, Cuba, Dominican Republic, Ecuador, Panama, Paraguay, Peru and Uruguay.

HIV prevalence in women giving birth in Catalonia continue to occur predominantly in women born abroad coming from countries with high HIV prevalence (ie: Sub-Saharan Africa) mirroring the situation of their country of origin.

The new Spanish legislation²³ denying health assistance to migrants without residence permit may reduce accessibility of vulnerable women to care aggravating the situation of coming years. Further studies should be developed to ascertain entrance and retention to care of these HIV infected women giving birth.

This paper, as well as other studies⁴, underlines the value of studying populations' origins in monitoring HIV prevalence in diverse populations as well as the need to ensure reaching these populations on time.

What is known about the topic?

HIV unlinked anonymous testing of neonatal dried blood spots taken for metabolic screening is simple, cheap and has the added advantage of providing unbiased prevalence rates. From 1994 to 2007 there has been a declining trend of HIV prevalence among women giving birth in Catalonia.

What does this study add to the literature?

From 2008 onwards highest HIV prevalence rates were among women born in Sub-Saharan Africa or Latin America and living in Barcelona City and cities \leq 200,000 inhabitants. Therefore, antenatal and postnatal care should be maintained and strengthened with special attention to ascertain entrance and retention to care, addressing cultural and language barriers of these HIV infected women giving birth.

Editor in charge

Pere Godoy.

Authorship contributions

Conceived and designed the study

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Performed the study

Jose Luis Marin, Carmen Martinez, Victoria Gonzalez and Rafael Muñoz

Analysed data

Dolors Carnicer-Pont and Alexandra Montoliu

Wrote and commented the manuscript

Dolors Carnicer-Pont, wrote the article and **Mireia Jane and Jesus Almeda gave critical inputs and a valuable intellectual contribution.** The remaining authors also commented on the manuscript.

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Conflicts of interest

None of the authors has a conflict of interest.

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Appendix A. The members of the HIV nadó working group

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