

A population-based evaluation of the impact of antenatal screening for Down's syndrome in France, 1981 - 2000

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## **Abstract**

*Objective:* To evaluate the impact of policy and practice changes in prenatal screening for Down's syndrome(DS) on prenatal diagnosis and livebirth prevalence of DS.

*Design:* Population-based observational study.

*Setting:* Greater Paris.

*Population:* Residents of Greater Paris who gave birth or had a termination of pregnancy in Paris during 1981-2000(~38,000 births per year).

*Main outcome measures:* Trends in proportion of DS cases diagnosed prior to birth; livebirth prevalence of DS.

*Methods:* Data on 1916 cases of DS were obtained from the Paris Registry of Congenital Anomalies. Analyses included binomial and Poisson models of trends in three periods: prior to 1989(reference period), 1989-1995(reimbursement of amniocentesis in case of ultrasonographic anomalies), and 1996-2000(widespread use of reimbursed serum screening and measurement of nuchal translucency).

*Results:* The proportion of DS detected prenatally for women <38 years of age increased nine-fold; from 9.5%(95%CI, 2.7-22.6) in 1981 to 84.9%(95%CI, 74.6-92.2) in 2000. For women  $\geq$ 38 years of age, the increase was 1.5-fold. The livebirth prevalence of DS decreased by 3% per year(Prevalence Ratio 0.97, 95%CI, 0.96-0.99); the age-adjusted decrease was 13%. The analysis by period showed that the decrease in livebirth prevalence of DS was greater after 1988.

*Conclusions:* By far most cases of DS are currently detected prenatally in the Parisian population. Consequently, the livebirth prevalence of DS has decreased despite consistent trends towards delayed childbearing. These positive public health effects have to be balanced against a relatively high rate of amniocentesis and the potentially negative consequences of widespread prenatal testing for individuals born with DS.

## Introduction

Prenatal diagnosis for Down's syndrome has made considerable progress in the past twenty years<sup>1;2</sup>. In particular, techniques using maternal serum and ultrasonographic markers have provided non-invasive antenatal screening tests for Down's syndrome. This has been especially important for younger women who are at lower risk of Down's syndrome, and hence usually not candidates for invasive diagnostic procedures, but who nevertheless often account for the majority of Down's syndrome cases due to the size of their population.

Along with technical progress in antenatal screening, public policies on screening have been adopted in several European countries<sup>3</sup>. In particular, a policy of general offer of serum screening for all women is to be implemented in England in 2004<sup>4</sup>. France has pursued an active national policy for prenatal screening of Down's syndrome<sup>5;6</sup>. In recent years, prenatal diagnosis of Down's syndrome has expanded considerably from a system essentially based on offering amniocentesis to women 38 years of age or those with significant family history of chromosomal abnormalities to a regulated system of universal access to both ultrasound and maternal serum screening. This process came about as a result of important changes in the policy for prenatal testing introduced in 1988 with increasing use of ultrasound and reimbursed amniocentesis in case of ultrasound abnormalities suggesting the presence of a chromosomal anomaly and the introduction of maternal serum screening in the early 1990's with its widespread use after 1997. Finally, the use of nuchal translucency measurement became widespread beginning in 1996.

The current policy for antenatal screening in France includes: i) nuchal translucency measurement as a matter of routine between 11-13 weeks of gestation, ii) maternal serum screening between 14 and 16 weeks (cut-off level 1/250), which should be systematically proposed to all women as stated by a law implemented in January 1997, and iii) a morphological scan at around 22 weeks of gestation for all women. Costs of antenatal

screening are reimbursed and in the case of a positive result in any of the screening tests, amniocentesis is proposed and its costs are reimbursed. In addition, reimbursed amniocentesis (or chorionic villus sampling) is available to all women 38 years of age and older. In the event of a prenatal diagnosis of Down's syndrome, or in general any "serious illness, recognised as incurable at the time of diagnosis"<sup>7</sup>, termination of pregnancy is allowed regardless of gestational age.

The primary goals of this policy are to increase prenatal detection of Down's syndrome in order to maximise the options available to pregnant women and to allow an informed choice about prenatal testing<sup>8</sup>. Few studies have evaluated the impact of these policies at the population level<sup>6;9</sup>, and in particular none have assessed the impact of the recent changes in antenatal screening policy on the detection rates and the livebirth prevalence of Down's syndrome.

Paris Registry of Congenital Anomalies was established in 1981 for the surveillance of birth defects in the Parisian population. It is a population-based registry, and a member of the European network EUROCAT, and of the International Clearinghouse for Birth Defects Monitoring Systems (IBCDMS). Because of the availability of data for a period of twenty years, completeness of ascertainment including terminations of pregnancy, and comparability of data from one year to the next, this database can be used to evaluate the population-level impact of antenatal screening for Down's syndrome.

The objective of this study is to evaluate the impact of prenatal screening for Down's syndrome in the Parisian population in terms of trends in: i) the proportion of Down's syndrome cases detected prenatally, and ii) the livebirth prevalence of Down's syndrome, in relation to important changes in the policies for prenatal screening during 1981-2000.

## Material and Methods

Data were obtained from the Paris Registry of Congenital Anomalies. The study population included all cases of trisomy 21 among the residents of Greater Paris who either gave birth or terminated a pregnancy in Paris maternity units (approximately 38,000 births per year). Data for the Registry are collected from multiple sources of information, including maternity units, neonatology services, cytogenetic and pathology services, in order to allow high case ascertainment for malformations and chromosomal abnormalities.

During the study period, among a total number of 738,668 births, 1916 cases of Down's syndrome, including live births, still births (at least 22 weeks after the last menstrual period), and terminations of pregnancy after prenatal diagnosis (regardless of the gestational age) were reported. The denominators were obtained from the French National Institute of Statistics (INSEE). Maternal age distribution of women giving birth within the population covered by the registry was also obtained from the same source. For each case, data on sociodemographic factors, utilisation of antenatal screening and diagnosis were collected. Maternal age was missing for 15 cases (0.8%). Data for prenatal testing were not available for the first two years of the registration. Therefore, the proportion of cases detected prior to birth was calculated only for the period 1983-2000. During this period, data on prenatal testing were missing for 5 cases (0.3%). Miscarriage cases were excluded in the analysis of trends for the proportion of cases detected prior to birth.

Total prevalence was calculated as the total number of Down's syndrome cases (live births + stillbirths + terminations of pregnancy) per 10,000 births. Live birth prevalence was defined as the number of Down's syndrome live births per 10,000 live births. Cases considered detected prior to birth included all those with prenatal cytogenetic confirmation, as well as, 32 cases diagnosed after birth for which results of ultrasound and/or serum screening

had suggested the need for an amniocentesis, which nonetheless was not undertaken based on women's wishes.

### Statistical Analysis

We used binomial regression models<sup>10</sup> to assess time trends in the proportion of Down's syndrome cases detected prior to birth. Maternal age-adjusted risk ratios with 95% confidence intervals were calculated to compare the probability of Down's syndrome detected prior to birth in the three periods corresponding to major changes in the practice and policy of prenatal testing in France: 1) prior to 1989, cytogenetic examination for high risk groups (maternal age  $\geq 38$  years, family history of Down's syndrome or relevant translocations); 2) 1989-1995, reimbursement of amniocentesis in case of ultrasonographic anomalies; 3) 1996-2000, widespread screening with nuchal translucency measurement and maternal serum screening.

We used Poisson regression models<sup>11</sup> to analyse time trends in total and live birth prevalence of Down's syndrome. In the analysis of trends in total prevalence of Down's syndrome, expected foetal loss rate after prenatal diagnosis was adjusted using estimates suggested by Cuckle<sup>12</sup>.

We assessed the overall annual trends, as well as, piece-wise linear estimates of the annual trends in the livebirth prevalence of Down's syndrome in the three periods 1981 – 1988, 1989 – 1995 and 1996 – 2000. Marginal piecewise coefficients were obtained, which represent the change in the slope from the preceding period; e.g., change in the annual trend in live birth prevalence observed in 1989 – 1995 as compared with 1981 - 1988. Goodness-of-fit tests were done to assess evidence of any overdispersion (extra-Poisson variation). We did not find any evidence of significant lack of fit. Results of the annual trends in the total and live birth prevalence of Down's syndrome are reported in terms of prevalence ratios (PR) with

95% confidence intervals. All statistical analyses were done using the STATA<sup>13</sup> statistical software.

## Results

### *Trends in the proportion of cases detected prior to birth*

Overall, the proportion of cases of Down's syndrome that were detected prior to birth increased by about nine-fold for women < 38 years of age; from 9.5% (95% CI, 2.7-22.6) in 1983 to 84.9% (95% CI, 74.6-92.2) in 2000. For women 38 years of age and older, the proportion of cases detected prior to birth increased by about 1.5-fold; from 59.1% (95% CI, 36.4-79.3) in 1983 to 95.4% (95% CI, 87.1 – 99.0) in the year 2000 (Table 1). Hence, compared to the period 1983-1988, the probability of a Down's syndrome case being detected prior to birth for women less than 38 years of age increased by 3.2-fold (age-adjusted Risk Ratio (RR), 3.2, 95% CI, 2.4 – 4.2) in the period 1988-1995 and by 4.5-fold (age-adjusted RR, 4.5, 95% CI, 3.4 – 5.9) in the period 1996-2000 (Table 2). For women 38 years of age or greater, the rate of increase in the probability of a case being detected prior to birth was 1.1 and 1.2-fold for the two periods, respectively (age-adjusted risk RR, 1.1, 95% CI, 1.0 – 1.2 in 1989-1995, and age-adjusted risk RR, 1.2, 95% CI, 1.1 – 1.3, in 1996 – 2000). However, women 38 years of age or greater had much higher proportions of cases of Down's syndrome detected prior to birth to begin with (Table 1). The net effect of these trends was that the proportion of cases of Down's syndrome detected prior to birth in women less than 38 years of age approached that of women 38 years of age or greater by the year 2000 (Figure 1).

### *Trends in total and live birth prevalence of Down's syndrome (Figure 2)*

During the study period, there was a substantial trend towards delayed childbearing in the study population. For example, the proportion of women  $\geq$  35 years of age increased from 11.1% (95% CI, 10.8 – 11.4) in 1981 to 26.1% (95% CI, 25.7 – 26.5) in 2000. Total prevalence of Down's syndrome increased on average by about 5% per year (Prevalence Ratio (PR), 1.05, 95% CI, 1.04 – 1.06). This increase could be explained by the increase in maternal



age and the higher rate of detection of Down's syndrome fetuses that would have been lost between the period of prenatal diagnosis and birth (age- and foetal loss rate-adjusted PR, 0.97, 95% CI, 0.90 – 1.05).

The live birth prevalence of Down's syndrome decreased by about 3% per year during this period (PR, 0.97, 95% CI, 0.96 – 0.99). After adjustment for the increase in maternal age, the magnitude of this decrease became approximately 13% per year (age-adjusted PR, 0.87, 95% CI, 0.78 – 0.98). We also assessed the trend in the live birth prevalence of Down's syndrome separately for the periods 1981-1988, 1989-1995, and 1996-2000. Piecewise linear estimates of the period trends suggested that a significantly greater decrease occurred in the live birth prevalence of Down's syndrome for the period 1989 – 1995 (age-adjusted PR, 0.89, 95% CI, 0.80 – 0.99) as compared with 1981 – 1988; the rate of decrease was not significantly different between 1989 – 1995 and 1996 – 2000 (age-adjusted PR, 0.97, 95% CI, 0.85 – 1.11).

## Discussion

In summary, the proportion of Down's syndrome cases detected prenatally increased substantially in the past two decades. This was particularly the case for younger women. By far most of the cases of Down's syndrome were detected prior to birth by the year 2000. Consequently, the live birth prevalence of Down's syndrome decreased in the 1990s despite the consistent trends towards delayed childbearing<sup>14</sup>. Taken together these trends suggest that the progress in screening techniques, together with the active national policy for antenatal screening in France, have had a major impact both on prenatal detection and the livebirth prevalence of Down's syndrome.

Recently, it has been suggested that maternal serum screening and ultrasound might preferentially detect fetuses that are lost prior to birth<sup>15</sup>. Hence, the impact of screening on

live birth prevalence of Down's syndrome might be lower than would otherwise be predicted. In our study, the crude (unadjusted) live birth prevalence of Down's syndrome decreased on average by about 3% per year over the study period; but live birth prevalence did not change appreciably before 1990. It should be noted however that these trends came about against the background of consistent increases in delayed childbearing and consequently simultaneous increases in the total birth prevalence of Down's syndrome. This was also reflected in the age-adjusted estimate of the annual rate of decrease in live birth prevalence of Down's syndrome, which was 13% as compared with 3% for the unadjusted estimate. Hence, notwithstanding the possibility of a preferential detection by prenatal screening of foetuses that are lost prior to birth, our results suggest that there was a major impact on live birth prevalence of Down's syndrome as a result of the increases in prenatal detection of Down's syndrome.

An important caveat that needs to be considered in the interpretation of our findings is that as an observational study of time trends, our study cannot establish a definitive causal link between the adopted policies and the rate of increase in prenatal detection of Down's syndrome. However, considering the particularly high rate of increase in the prenatal detection of Down's syndrome among younger women, it seems reasonable to assume that the progress in the ultrasonographic and maternal serum techniques for antenatal screening together with the policies adopted to ensure equal access to reimbursed screening for all women in France have had a major impact on prenatal detection of Down's syndrome. The effects of the policy however might differ across geographic regions in France as the amniocentesis rates are higher in Paris than in the rest of the country<sup>16;17</sup>.

Another caveat is that our study population might have changed over time in ways that might significantly affect our findings. In order to assess the possible impact of any such bias (including referral bias), we examined the trends in prenatal detection of Down's syndrome by limiting the study population to residents of Paris who gave birth or had a termination of

pregnancy in Parisian maternity units (i.e., excluding both women from the surrounding suburbs in the Greater Paris area and elsewhere). The results of these analyses of trends in prenatal detection of Down's syndrome were essentially identical to those presented here for the Greater Paris area.

In addition to its impact on detection rates or live birth prevalence, a complete evaluation of a screening policy also requires consideration of the costs of the program, including the rate of invasive diagnostic procedures and the associated risks of foetal loss. Our data do not allow evaluation of trends in these indices, in particular in the amniocentesis rates. Recent data suggest that the rate of amniocentesis is approximately 11% in France<sup>16</sup> and 16% in the Parisian population<sup>17</sup>. These rates are substantially higher than those reported for England<sup>4</sup> and the United States<sup>18</sup>.

It has been suggested that introduction of antenatal screening might provide an opportunity for decreasing the rate of amniocentesis, particularly among older women<sup>19;20</sup>. However, many women in France who are eligible for reimbursed serum screening, and in particular those with higher levels of education, obtain amniocentesis without serum screening<sup>21</sup>. This might limit the use of antenatal screening as a solution to the growing number of amniocenteses. However, as the sensitivity of prenatal screening strategies increases<sup>1</sup>, pregnant women might be increasingly likely to use antenatal screening and forego an amniocentesis in case of negative screening results.

Broader considerations in the evaluation of antenatal screening programs include assessment of issues related to the potentially negative effects of widespread screening on the perceptions about individuals with Down's syndrome and the services that might be available for their care. Indeed, a critique of prenatal testing has been its potential for reinforcing discriminatory views about individuals with disabilities<sup>22</sup>. Concerns have also been raised about the choices and the services available to women who might not wish to opt for prenatal

testing, if such testing comes to be viewed as the norm<sup>23</sup>. Given our data and comparable findings from another population<sup>24</sup> that suggest almost 90% of the cases of Down's syndrome might currently be detected and often terminated prior to birth, future studies and policies should also address the potentially negative consequences of widespread use of prenatal testing for individuals born with Down's syndrome and other congenital anomalies.

## Conclusions

By far most cases of Down's syndrome are currently detected prenatally in the Parisian population. Consequently, the livebirth prevalence of Down's syndrome has decreased despite consistent trends towards delayed childbearing. These positive public health effects have to be balanced against a relatively high rate of amniocentesis and the potentially negative consequences of widespread prenatal testing for individuals born with Down's syndrome. Any such negative consequences should be balanced against the choices afforded to women and their families as a result of prenatal testing.

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Table 1 - Proportion of Down syndrome cases detected prior to birth<sup>‡</sup> - Paris Registry of Congenital Anomalies, 1983-2000

Year	Maternal age < 38 years			Maternal age ≥ 38 ans		
	N	%	95 % CI*	N	%	95 % CI*
1983	42	9.5	2.7 - 22.6	22	59.1	36.4 - 79.3
1984	39	15.4	5.9 - 30.5	24	66.7	44.7 - 84.4
1985	41	9.8	2.7 - 23.1	28	82.1	63.1 - 93.9
1986	49	20.4	10.2 - 34.3	28	82.1	63.1 - 93.9
1987	40	27.5	14.6 - 43.9	28	75.0	55.1 - 89.3
1988	46	19.6	9.4 - 33.9	30	80.0	61.4 - 92.3
1989	57	36.8	24.4 - 50.7	47	74.5	59.7 - 86.1
1990	56	53.6	39.7 - 67.0	47	89.4	76.9 - 96.5
1991	63	39.7	27.6 - 52.8	49	91.8	80.4 - 97.7
1992	61	60.7	47.3 - 72.9	34	88.2	72.6 - 96.7
1993	61	62.3	49.0 - 74.4	43	86.0	72.1 - 94.7
1994	64	67.2	54.3 - 78.4	35	85.7	69.7 - 95.2
1995	51	64.7	50.1 - 77.6	53	94.3	84.3 - 98.8
1996	74	67.6	55.7 - 78.0	56	92.9	82.7 - 98.0
1997	83	79.5	69.2 - 87.6	62	93.5	84.3 - 98.2
1998	83	72.3	61.4 - 81.6	59	91.5	81.3 - 97.2
1999	73	90.4	81.2 - 96.1	57	94.7	85.4 - 98.9
2000	73	84.9	74.6 - 92.2	65	95.4	87.1 - 99.0

\* 95% binomial exact confidence interval

<sup>‡</sup> Miscarriage cases were excluded.



Table 2 - Trends in the proportion of Down syndrome cases detected prior to birth<sup>‡</sup> - Paris Registry of Congenital Anomalies, 1983-2000

Period	Maternal age < 38 years		Maternal age ≥ 38 ans	
	Adjusted RR*	95 % CI	Adjusted RR*	95 % CI
1983-1988	1.00	Reference	1.00	Reference
1989 - 1995	3.2	2.4 - 4.2	1.1	1.0 - 1.2
1996 - 2000	4.5	3.4 - 5.9	1.2	1.1 - 1.3

\* 95% Maternal age-adjusted risk ratio

<sup>‡</sup> Miscarriage cases were excluded.

Figure 1 - Three year moving average trends in the proportion of Down's syndrome cases detected prior to birth, Paris Registry of Congenital Malformations, 1983 - 2000. Arrows indicate the years (1988 and 1996) in which important changes took place with regard to prenatal testing policy in France (see text for additional details).

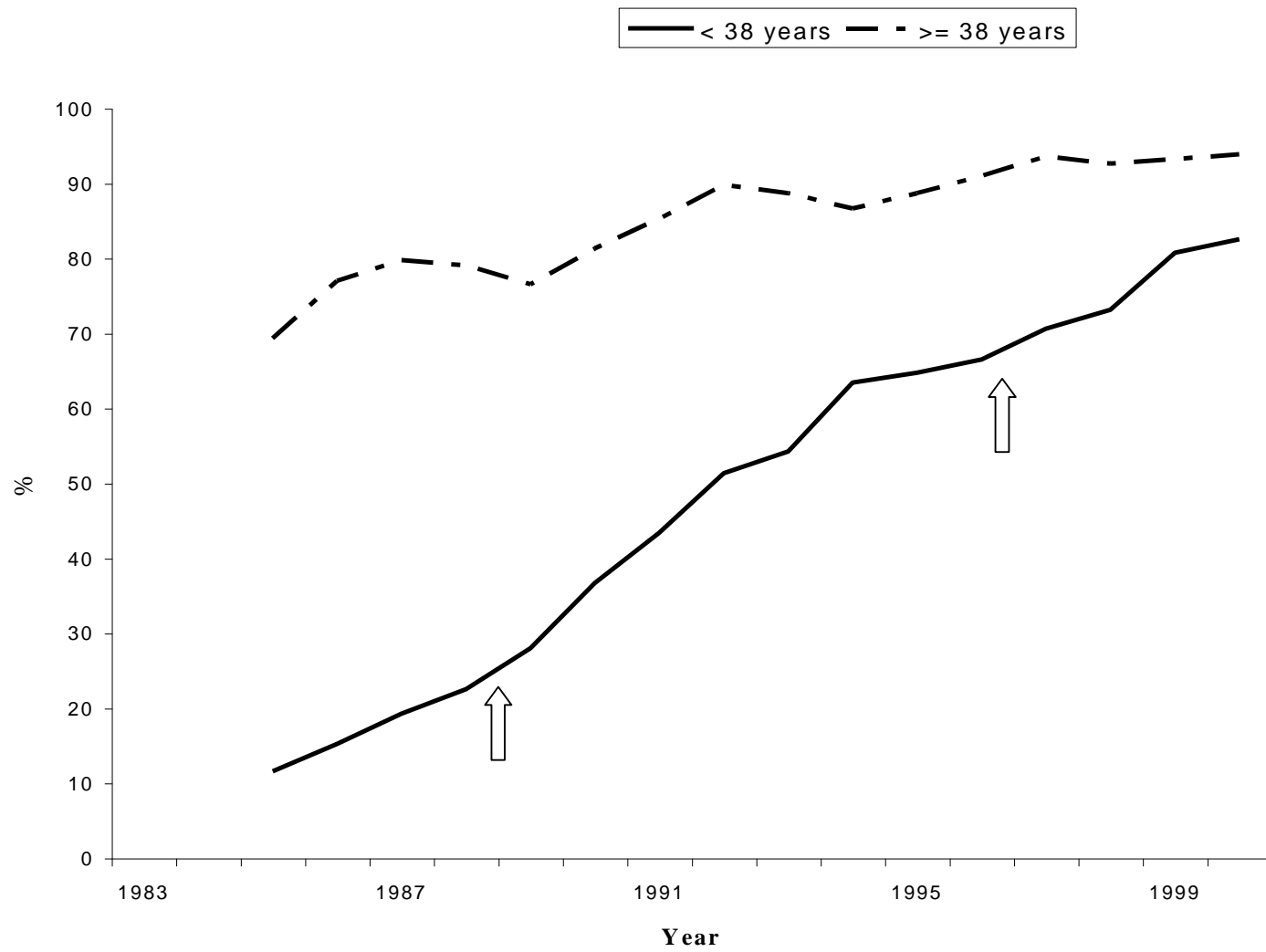


Figure 2 - Trends in prevalence of Down's syndrome, Paris Registry of Congenital Malformations, 1981 – 2000.

