

# The impact of introducing combined first-trimester trisomy 21 screening in the French population

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**Background:** French state health insurance has funded trisomy 21 prenatal screening for all pregnant women since decades. First-trimester combined screening was introduced nationally and funded in 2010. **Objective:** To evaluate the impact of the introduction, of a national policy of prenatal trisomy 21 first-trimester screening on the reduction of invasive prenatal diagnostic procedures. **Methods:** The results of all prenatal trisomy 21 screening and invasive diagnostic procedures were collected for the whole country over the period 2009–12. The screen-positive rates (risk cut-off 1 : 250, including isolated nuchal translucency  $\geq 3.5$  mm), positive predictive values and percentage of cases diagnosed prenatally were calculated. **Results:** Over the study period the number of women undergoing serum screening (including first- and second-trimester screening tests) increased from 678 803 to 689 651 (83 to 85% of deliveries,  $P < 0.0001$ ). By 2012, first-trimester combined screening accounted for 70% of all trisomy 21 screening. The screen-positive rate decreased from 9.5 to 4.8% ( $P < 0.001$ ) resulting in a 37 478 (47%) drop ( $P < 0.001$ ) in the number of invasive diagnostic procedures. The positive predictive value of screening increased from 2.6 to 6.1% from 2009 to 2012 ( $P < 0.001$ ), due to the higher positive predictive value of first-trimester over second-trimester screening (9.1 vs. 1.8% over the period 2010–12,  $P < 0.001$ ). The percentage of prenatally diagnosed cases remained high at around 80% between 2010 and 2012. **Conclusions:** The policy shift from second-trimester to first-trimester trisomy 21 screening allowed to reduce the number of invasive tests. The number of antenatal trisomy 21 diagnoses increased (+2.7%) over the study period.

## Introduction

Trisomy 21 screening has been routine prenatal care in France for many years. However, methods have changed over time. From 1980 to 1996, screening was based on maternal age alone and/or on the detection of foetal anomalies during the routine second-trimester ultrasound scan. As of 1997, screening was based on second-trimester maternal serum markers (MSMs) combined with maternal age<sup>1</sup> and in the late 1990s nuchal translucency (NT) measurement was also introduced although NT and MSM were rarely combined. In 2007, the French National Authority for Health (la Haute Autorité de Santé) published guidelines for Trisomy 21 prenatal screening and diagnosis that recommended combined first-trimester screening (combining maternal age with PAPP-A, hCG $\beta$  and NT) and no longer recommended karyotyping due solely to maternal age. National health insurance covered combined first-trimester T21 screening as of 2010.

The Agence de la biomédecine (<http://www.agence-biomedecine.fr/About-us>) is the French public agency which promotes, regulates and evaluates activities in four fields: organ, tissue and cell donation and transplantation, assisted reproductive technology, human embryology and genetics. It is the competent authority in France in charge of the medical, scientific, legal and ethical issues in these fields. As such, it was instructed to assess the impact of the implementation of newly established combined screening test.

The aim of this study is to monitor the French organization of trisomy 21 screening at a national level and to evaluate the impact of both the introduction of the combined first-trimester screening test and the elimination of maternal age as a criterion for foetal karyotyping.

## Methods

### Population and screening

This study was conducted during 2009–12 using the French nationwide anonymized database of maternal screening tests for trisomy 21 and foetal karyotypes. Prenatal diagnosis laboratories are authorized by the regional health authorities. These laboratories are required to report their activity to the ‘Agence de la biomédecine’ annually. Cytogenetic laboratories report all foetal karyotypes by indication and results. From 2010 onward, karyotypes of neonates affected by trisomy 21 diagnosed postnatally were also reported. Biochemistry laboratories report the total number of trisomy 21 screening tests carried out in France, by age group and type of testing, i.e. combined first-trimester screening tests, second-trimester serum screening and sequential tests combining first-trimester NT with second-trimester serum marker screening. These data were used to evaluate the impact of the introduction of first-trimester combined screening nationwide in 2010.

Prior to 2010, national health insurance covered foetal karyotyping indicated by a maternal age of 38 or older, or a second-trimester screening risk of over 1 : 250, or any structural defect detected by ultrasound (including increased nuchal translucency) or in cases with a history of chromosomal anomalies.

The 2007 national guidelines recommended that trisomy 21 screening be based on first-trimester screening combining maternal age, PAPP-A, hCG $\beta$  and NT measured by a trained professional at a crown rump length of 45–84 mm (the ‘first-trimester combined test’). If serum markers had not been sampled before 14 weeks, integrated second-trimester screening was recommended based on the combination of maternal age, AFP, hCG $\beta$  and NT (the ‘sequential test’). For late bookers or when no adequate NT measurement was available,

second-trimester screening was recommended based only on maternal age, AFP and hCG $\beta$  (the 'second-trimester test').

In 2010, national health insurance covered the costs of antenatal invasive diagnosis in all the earlier indications or when structural anomalies were found by ultrasound or when there was a history of chromosomal anomalies. Karyotyping was also recommended and reimbursed for isolated NT  $\geq 3.5$  mm. However, karyotyping for maternal age and contingent screening was discouraged, and no longer covered by national health insurance. As for serum screening, a 1 : 250 risk at birth cut-off was used in first- and second-trimester screening. Foetal structural abnormalities detected by ultrasound at any gestational age justify offering karyotyping irrespective of prior screening results.

Internal and external quality control of markers and risk calculation was mandatory. Reagents, automata and software for maternal serum screening all had to be provided by the same manufacturer. Four manufacturers were able to meet this condition: PerkinElmer (Turku, Finland), Roche Diagnostics (Basel, Switzerland), Siemens (Tarrytown, NY) and ThermoFisher (Hennigsdorf, Germany). The combination of ultrasound and serum markers to evaluate risk was based on algorithms provided by each manufacturer.

Serum screening laboratories are subject to accreditation. Of the 4300 laboratories in France, 82 are accredited for T21 screening and all 70 cytogenetic laboratories are accredited for foetal karyotyping. In application of French law, biochemical blood sample analysis during routine antenatal care can only be done if the woman has given prior informed consent. However, amongst the women who were not screened, it is not possible to distinguish between those who did not give consent and those who were not aware of the possibility of being screened. A second written consent was given for foetal karyotyping if chorionic villus sampling or amniocentesis was carried out.

As of 2009, a national policy was introduced to encourage sonographers to train in NT measurement. The approach drew on several training programs, promoting NT measurement as described by the Fetal Medicine Foundation<sup>2</sup> or the Collège d'échographie foetale.<sup>3</sup> Having undergone training in NT measurement, sonographers submitted NT images to one of the three accredited control programs<sup>3</sup> for validation. On validation, they were attributed an identification number by their local perinatal network. This number is required to be allowed to carry out combined screening. Antenatal ultrasound scans are performed mainly by physicians and to a lesser extent by midwives and it took two years develop the required NT measurement capacity of 5000 accredited sonographers. Continuous quality control is mandatory and under the responsibility of each of the 46 regional perinatal networks. The physician in charge of prescribing the screening will interact with biochemistry and cytogenetic laboratories. Any decision concerning a foetal abnormality will rely on one of the 49 multidisciplinary prenatal diagnosis centres appointed by the ministry of health to which the management of all foetal abnormality cases must be referred. In 2010, 3252 sonographers performed at least one NT measurement in the context of first-trimester

combined screening, and there were 1012 newly accredited sonographers in 2011 and 548 in 2012.

## Statistics

The impact of the implementation of first-trimester combined screening was evaluated by comparing changes in key indicators of prenatal screening and diagnosis over the study period, 2009 was the reference year.

The number of deliveries and total number of births in France during the study period were extracted from INSEE data.<sup>4</sup> The expected number of live births with trisomy 21 in the absence of screening was estimated from the number of newborns, maternal age and the maternal age-related risk of birth with trisomy 21.<sup>5</sup> This estimation is lower than the total number of antenatal and postnatal diagnoses observed due to the high rate of miscarriage of fetuses with trisomy 21.<sup>6,7</sup> The evolution of the number of predicted and observed affected live births during the period was observed.

Cytogenetic laboratory foetal karyotype results provide the number of invasive diagnostic procedures performed and allow the estimation of the positive predictive value (PPV) of the screening tests. A diagnostic test (chorionic villus sampling or amniocentesis) was recorded for 64% of the screen-positive women and the PPV was estimated in that sample.

The evolution of the percentages of cases diagnosed prenatally was observed at national level regardless of whether or not and of what type of screening was used.

Screening results over a 1 in 250 probability of the foetus being affected or with NT measurements of 3.5 mm or more were categorized as 'high risk'. The high-risk cohort was considered as the screen-positive group and its size considered as the screen-positive rate. The screen-positive rates were estimated using the data provided by the biochemistry laboratories.

Chi squared tests were performed to compare percentages and 95% confidence intervals (CI<sub>95%</sub>) were estimated for rates.

## Results

In France, the predicted prevalence of trisomy 21 live births in the absence of screening increased from 0.239% CI<sub>95%</sub> [0.223–0.25] to 0.248% CI<sub>95%</sub> [0.237–0.259] (+3.8%,  $P=0.25$ ) over the study period, due to the increase in maternal age. The number of live births decreased from 834 622 to 829 508 whereas the expected number of affected live births increased from 1997 to 2057 (+3%) (table 1). The observed prevalence of trisomy 21 live births varied from 0.54 per 1000 births CI<sub>95%</sub>[0.49–0.59] in 2010 ( $n=453$ ) to 0.59 CI<sub>95%</sub>[0.54–0.64] in 2012 ( $n=488$ ) ( $P=0.17$ ).

The percentage of women who opted for prenatal trisomy 21 screening also increased slightly during the study period from 83 to 85% ( $P<0.0001$ ). In 2010, first-trimester combined screening was used in 41% of tests reaching 70% in 2012 (table 3). The screening procedure followed by women in 2012 is shown in figure 1.

Introducing combined first-trimester screening reduced the number of invasive diagnostic tests by 37 478 decreasing from 9.6

**Table 1** Evolution of births in France

	2009	2010	2011	2012
Deliveries: <i>N</i>	820 970	826 703	816 948	815 406
Total births: <i>N</i>	834 622	841 563	831 512	829 508
Maternal age: mean	29.9	29.9	30.0	30.1
Maternal age: %				
<35	78.4%	78.5%	78.4%	78.3%
35–37	12.4%	12.0%	11.7%	11.8%
>37	9.2%	9.5%	9.9%	9.9%
Expected live births with trisomy 21 <sup>a</sup> : <i>N</i>	1997	2035	2047	2057
Expected live births with trisomy 21 <sup>a</sup> : % births	0.239%	0.242%	0.246%	0.248%

a: number of live born babies with trisomy 21 in the absence of screening and subsequent termination.<sup>5</sup>

to 5.1% ( $P < 0.001$ ) of all pregnancies. At the same time, the number of women over 38 years with an invasive diagnostic test without prior screening dropped by 90% ( $n = -21\,145$ ). The number of foetal karyotypes performed due solely to increased NT ( $\geq 3.5$  mm) dropped by 36% ( $n = -1909$ ) (table 2).

The number of antenatal trisomy 21 diagnoses increased from  $N = 1918$  to  $N = 1970$  (+2.7%) over the study period. The overall number of ante and postnatal trisomy 21 diagnoses increased by 3% from 2387 to 2458 in 2012 following the same pattern as the number of cases that would be expected in the absence of screening. The percentage of cases diagnosed prenatally varied from 81% in 2010 to 78% in 2011 ( $P = 0.02$ ) and 80% in 2012 ( $P = 0.44$  for 2012 vs. 2010) (table 2). The prevalence of other unbalanced chromosomal anomalies diagnosed prenatally remained quite stable over the study period from 2.51 per 1000 births [2.40–2.62] ( $n = 2098$ ) in 2009 to 2.52 ( $n = 2094$ ) in 2012; the prevalence of trisomy 18 and 13 was 1.01 per 1000 births in 2009  $CI_{95\%}[0.94-1.08]$  vs. 1.10 in 2012  $CI_{95\%}[1.03-1.17]$  ( $P = 0.08$ ).

At national level, the screen-positive rate decreased from 9.5% in 2009 to 4.8% in 2012 ( $P < 0.001$ ). This could be explained by the increased use of first-trimester combined tests which have a lower screen-positive rate of 4.1% than to second-trimester screening tests at 8.9% ( $P < 0.001$ ). The screen-positive rate of first-trimester combined tests decreased from 5.1 to 3.8% ( $P < 0.001$ ) from 2010 to 2012 while that of second-trimester tests increased from 8.7 to 9.8% ( $P < 0.001$ ) over the same period (table 3). The high screen-positive rate (34%) of first-trimester combined tests observed in

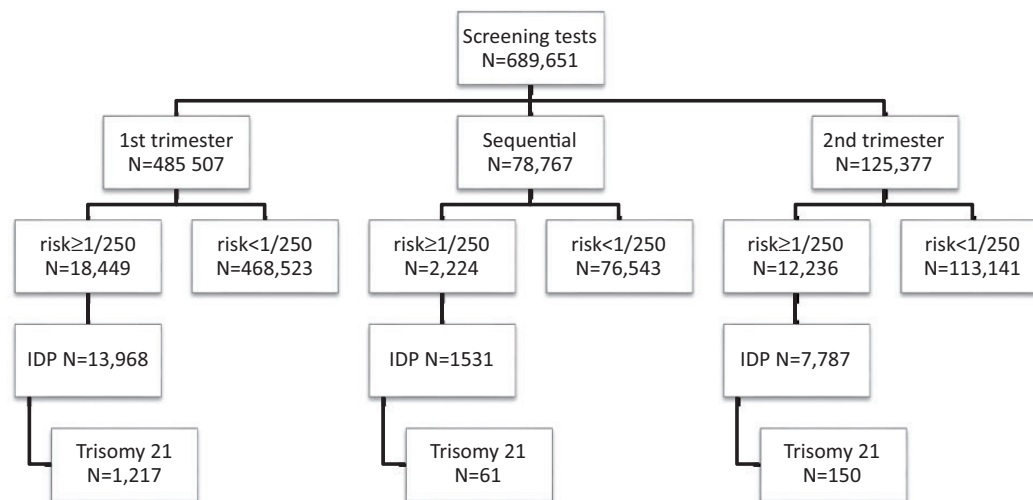
2009 can be explained by its restricted use during that period in a highly selected population, with one-third of the cases having an NT measurement of 3.5 mm or more. The sample of women who had combined first-trimester screening in 2009 was not therefore representative of the general population of pregnant women as this screening was only proposed in a few centres to which high-risk patients were referred.

The PPV of screening tests increased from 2.6 to 6.1% between 2009 and 2012 ( $P < 0.001$ ). This rise was mainly related to the increased use of first-trimester combined tests with a PPV of 9.2% replacing serum marker second-trimester tests with a PPV of 1.8% ( $P < 0.001$ ) over the 2010–12 period (table 4). The first-trimester combined test PPV was not stable over the period decreasing from 10 to 8.7% ( $P < 0.001$ ).

In 2012, 72% ( $n = 1428/1970$ ) of antenatal diagnoses of trisomy 21 followed on from routine screening (including NT  $\geq 3.5$  mm) compared with 52% ( $n = 1007/1918$ ) in 2009.

## Discussion

The results show that access to routine trisomy 21 screening remained stable during the study period, and that first-trimester combined screening accounted for 70% of all trisomy 21 screening in 2012. At a national level, the screen-positive rate decreased significantly (from 9.5 to 4.8%) resulting in a 47% reduction in the number of invasive diagnostic procedures. With foetal loss estimated between 0.5 and 1%<sup>8</sup> after invasive diagnosis then between 187 and 374 losses were avoided



**Figure 1** Flow chart of the screening procedures in 2012. First trimester = combined test (NT and MSM) and NT  $\geq 3.5$  mm alone. Sequential = first-trimester NT and second trimester MSM. Second trimester = MSM alone. IDP, invasive diagnostic procedure

**Table 2** Evolution of invasive diagnostic procedures and diagnosis of trisomy 21 in France

Invasive diagnostic procedure (IDP)	2009 <sup>a</sup>	2010	2011	2012
<i>N</i> (% deliveries)	79 105 (9.6%)	55 568 (6.7%)	45 043 (5.5%)	41 627 (5.1%)
- IDP for screen-positive test <sup>b</sup>	33 135	28 199	22 175	20 004
- IDP for NT $\geq 3.5$ mm alone	5359	4307	3628	3450
- IDP for women $\geq 38$ years	23 563	6615	3385	2418
- IDP for other ultrasound signs	12 140	12 017	11 404	11 536
- IDP for other indications	4908	4430	4451	4219
Total trisomy 21 pre and postnatally diagnosed: <i>N</i> (% births)	NA	2387 (0.286%)	2477 (0.294%)	2458 (0.296%)
Trisomy 21 prenatally diagnosed: <i>N</i>	1918	1934	1944	1970
% of total cases [ $CI_{95\%}$ ]	–	81.0% [79–83]	78.4% [77–80]	80.1% [79–82]

Data source = cytogenetic laboratories.

a: Reference year.

b: Excluding nuchal translucency (NT)  $\geq 3.5$  mm alone. NA, not available; IDP, Invasive diagnostic procedure;  $CI_{95\%}$ , 95% confidence limits.

**Table 3** Evolution of the screen-positive rates of trisomy 21 screening tests

Screening test	2009 <sup>a</sup>		2010		2011		2012	
	N	Screen-positive rate (%)	N	Screen-positive rate (%)	N	Screen-positive rate (%)	N	Screen-positive rate (%)
First-trimester <sup>b</sup>	18 174	34.0	295 108	5.1	457 821	3.8	485 507	3.8
% overall	2,7%		41,0%		65,4%		70,4%	
Sequential <sup>c</sup>			56 248	3.8	69 286	3.3	78 767	2.8
% overall			7,8%		9,9%		11,4%	
Second-trimester <sup>d</sup>	660 629	8.8	369 100	8.7	172 941	9.4	125 377	9.8
% overall	97,3%		51,2%		24,7%		18,2%	
Overall	678 803	9.5	720 456	6.9	700 048	5.2	689 651	4.8

Data source = biochemistry laboratories.

a: Reference year.

b: First trimester = combined test (NT and MSM) and NT  $\geq$  3.5 mm alone.

c: Sequential = first-trimester NT and second-trimester MSM.

d: Second trimester = MSM alone.

In 2009, first-trimester tests included 5359 NT  $\geq$  3.5 mm alone and 12 815 first-trimester combined tests performed in 'at risk' population.

**Table 4** Evolution of the PPV of trisomy 21 screening tests

Screening test	2009 <sup>a</sup>		2010		2011		2012	
	N	PPV (%)	N	PPV (%)	N	PPV (%)	N	PPV (%)
First-trimester <sup>b</sup>	NA	NA	9 509	10.0	12 540	9.0	13 968	8.7
Sequential <sup>c</sup>	–	–	1 686	3.3	2 063	2.6	1 531	4.0
Second-trimester <sup>d</sup>	NA	NA	16 587	1.7	9 928	1.9	7 787	1.9
Unknown type of tests	38 494	2.6	4 724	1.8	1 272	2.3	168	0.0
Overall	38 494	2.6	32 506	4.2	25 803	5.4	23 454	6.1

Data source = cytogenetic laboratories.

a: Reference year.

b: First trimester = combined test (NT and MSM) and NT  $\geq$  3.5 mm alone.

c: Sequential = First-trimester NT and second-trimester MSM.

d: Second trimester = MSM alone. PPV, positive predictive value; NA, not available.

each year. This is particularly clear in women over 38 who underwent prenatal screening instead of diagnosis, therefore avoiding 105–211 losses related to invasive procedures.

Assessment of the national introduction of prenatal combined first-trimester screening for trisomy 21 considered both its impact on access to prenatal screening and diagnosis and on the effectiveness of the screening tests. The evaluation could be considered accurate and robust due to the completeness of the data and the large population size over the four year period. However, the lack of information on pregnancy outcomes prevented the appraisal of the actual prevalence of undetected trisomy 21 in miscarriage and the number of affected live births in the screened population. The expected number of foetuses with trisomy 21 over the screening period was estimated using maternal age-related risk, this method is robust when used in large numbers and it avoids the missing data due to lost to follow-up.<sup>5</sup>

There are many studies in the literature reporting the excellent performance of first-trimester combined screening.<sup>9</sup> However, very few studies report results at national level.<sup>10–13</sup> Based on the same risk cut-off 1 : 250, the screen-positive rate of 3.8% observed in 2012 in France is close to the 4% in the Finnish prospective study<sup>12</sup> and the 3.2% in the population of England.<sup>11</sup>

Clinicians and patients sought the reduction of invasive diagnosis to avert associated iatrogenic risk. In spite of the considerable reduction in invasive procedures, the percentage of prenatal trisomy 21 syndrome diagnosis has remained high at around 80%. Comparing results of different types of screening using MSMs clearly shows that first-trimester combined screening has a much higher PPV than second-trimester screening. As such, it should be preferred and sufficient means should be employed to offer it to all pregnant

women wishing T21 screening, including access to NT measurement. An increase in the detection of other serious chromosomal anomalies has also been observed. The extension of a screening method that involves a nuchal scan to the whole population, however, is not easily achieved as all sonographers' measurements need to be consistent throughout the country. Sonographer training and evaluation programmes have supported the widespread implementation of first-trimester combined screening and made it available to a large number of pregnant women.

The screen-positive rate and the PPV of the first-trimester combined screening decreased between 2010 and 2012 while the percentage of cases diagnosed prenatally relative to total cases actually diagnosed varied between 78 and 81% for the whole period. Whether such variations reflect the impact of the increasing competency of sonographers entering the screening program or the extension of the screening test to a population with different levels of background risk needs further evaluation. Specificities of software provided by manufacturers might also be a source of variation. The nationwide implementation of screening based on ultrasound measurements was a real challenge requiring a high level of training of professionals. However, the results are convincing and can be expected to improve in the coming years.

In conclusion, France has provided all resident pregnant women who so wish access to first-trimester combined Trisomy 21 screening on the national health insurance scheme since 1 January 2010. In order for all women to be able to benefit from this irrespectively of their location, it was necessary to train sonographers throughout the country and to effectively evaluate their professional practice. The role of the Agence de la biomédecine was to globally evaluate the new system and to compare it with the previous one. This study of

the system's performance from 2009 to 2012 shows that pregnant women, including those aged 38 and over, have extensively adopted and used this new form of screening. Its widespread extension has led to a significant reduction in the number of invasive diagnostics tests whilst maintaining an acceptable level of diagnosis in spite of minor variations.

Comparing different methods of screening clearly shows that the PPV is superior when NT measurement is taken into account and that combined first-trimester screening gives the best PPV.

The feasibility of the non-invasive testing of Trisomy 21 by high throughput sequencing of foetal DNA in maternal blood has been proved,<sup>14–18</sup> however, for the time being, several difficulties, not least its availability, prevent its use in place of combined first-trimester screening which will continue to be evaluated. Every pregnant woman should be made aware that she can choose Trisomy 21 screening if she so wishes and should be certain that the strategy that she is proposed has been and continues to be properly evaluated.

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## Key points

- The impact of the introduction of a national policy of prenatal trisomy 21 combined first-trimester screening was evaluated in the French population from 2009 to 2012.
- The policy shift from second-trimester to first-trimester trisomy 21 screening resulted in a 47% reduction in the number of invasive diagnostic procedures with between 187 and 374 losses being avoided each year. The number of antenatal trisomy 21 diagnoses increased from  $N=1918$  to  $N=1970$  (+2.7%) over the study period.
- These results confirm the robustness of combined first-trimester screening tests in large population.

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