National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Quality control parameters of Dutch Down's syndrome screening laboratories 2009 (2007-2008, when available)

RIVM report 230083002/2011

P.C.J.I. Schielen

National Institute for Public Health
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Colophon

P.C.J.I. Schielen (Head of Reference Laboratory Down's syndrome screening), National Institute for Public Health and the Environment-Laboratory for Infectious diseases and screening, on behalf of the Dutch Down's syndrome screening laboratories.

Contact:
Peter Schielen
National Institute for Public Health and the Environment-Laboratory for Infectious diseases and screening
Peter.Schielen@rivm.nl

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Abstract

Quality control parameters of Dutch Down's syndrome screening laboratories 2009 (2007-2008, when available)

This is the first report on the performance of Dutch screening laboratories with regard to Down's syndrome screening. Data were kindly provided by the seven screening laboratories and the evaluation was performed at the RIVM (housing the reference laboratory). The main achievement of this evaluation was to for the first time give the annual (2009) number of screening tests (48457), the participation of the pregnant population (25.7%), the median age of the participating pregnant women (32-33.5 years) and an impression of the proportion of high risk results for several regions (AMC-laboratory;6.3%, RIVM-laboratory; 4.8%, VUMC laboratory; 7.4% and MUMC laboratory; 5.4%). There were also notable differences in the gestational age at blood sampling (at about 10 weeks in some areas and 12 weeks in others).
The analytic performance was analysed by evaluating the concentrations of the serum parameters (pregnancy-associated plasma protein A; PAPP-A), the free β subunit of human choriongonadotropin (fβ-hCG) and the nuchal translucency (NT) measurement and secondary parameters, showing that mostly, these parameters were according to quality standards during 2009. As data of two other quality control programmes that all laboratories participate in were also according to standards, we conclude that no major problems occurred in 2009. For the future, we will try to produce a more complete record of all performance indicators, possibly with the aid of a national database, 'Peridos'.

Keywords:
Screening laboratories, quality assurance, Down's syndrome screening, first trimester combined test

Rapport in het kort

Kwaliteitsindicatoren van de Nederlandse downsyndroom screening laboratoria 2009 (deels 2007-2008)

Het RIVM heeft voor het eerst de prestaties van de Nederlandse downsyndroom-screeninglaboratoria geanalyseerd, en wel over het jaar 2009. Hieruit blijkt dat de tests naar behoren zijn uitgevoerd. De screening bestaat formeel sinds 1 januari 2007 en omvat twee bloedtests en een nekplooimeting. Met de evaluatie wordt voldaan aan de opdracht aan het referentielaboratorium om de kwaliteit van de screening te bewaken.

Voor de analyse hebben de zeven screeningslaboratoria, verspreid over Nederland, die de bloedtests uitvoeren hun data over 2009 beschikbaar gesteld; Een daarvan is het referentielaboratorium, dat is ondergebracht bij het RIVM.

Bevindingen
In 2009 zijn in totaal 48.457 screeningstests afgenomen; daarmee laat 25,7 procent van de zwangeren een dergelijke test uitvoeren. De leeftijd waarop de test het vaakst wordt afgenomen blijkt 32-33,5 jaar (mediane leeftijd). Het aantal zwangeren dat volgens de screeningtest een hoog risico loopt op een kind met het Downsyndroom is in het laboratorium van het AMC 6,3 procent, in het referentielaboratorium van het RIVM 4,8 procent, 7,4 procent bij het VUMC-laboratorium en 5,4 procent voor dat van het MUMC. De laboratoria blijken op uiteenlopende momenten de test af te nemen: in sommige regio's gebeurde dat vroeg in de zwangerschap, in week 10. In andere later, in week 12. Een vroeg afgenomen test geeft een betere indicatie.

Analyse bloedtests en nekpooimeting
Verder zijn de gemiddelde concentraties van de bloedtests geëvalueerd (van de stoffen PAPP-A en hCG-beta), evenals de uitslagen van de nekplooimeting (NT). Hieruit blijkt dat ze voldoen aan de kwaliteitscriteria die voor de screentests zijn opgesteld. Aanbevolen wordt de gegevens over de bloedtest voor de evaluatie aan te vullen met de ontbrekende gegevens over de nekplooimeting. Een eerste aanzet is daartoe in 2012 gemaakt door de landelijke database met deze gegevens, Peridos, voor deze analyse in te zetten.

Trefwoorden:
screening laboratorium, kwaliteitsborging, downsyndroom screening, 1e trimester combinatietest

Contents

1 Introduction

The Dutch national programme for Down's syndrome screening gained momentum between 2004 and 2006 and started formally on January 1, 2007.

Both the reports of the Dutch Health Council on the prenatal screening for Down's syndrome (1) and the letters to Parliament of State Secretary Ross van Dorp in 2004 and 2005 (2, 3), outlining the structure of the future Down's syndrome screening programme, stressed the importance of the programmes quality assurance. Limiting the number of screening laboratories to seven was one of the measures to meet this aim, enabling the rigid control of the quality of the screening test and because of the high number of analyses per laboratory, allowing for timely corrective action in case of an incident (4). The quality assurance guidelines for the screening test and the laboratories were formulated by the "Centraal Orgaan" (Central Agency), the main advisory board of the Centre for Population Research (RIVM), which is responsible for the organisation of the prenatal screening programme.

Since 2004, the Dutch ('candidate') screening laboratories have met frequently at 3-4 months intervals to discuss operational matters and especially, quality assurance and quality control issues. To minimise operational variations the laboratories agreed to all use the same equipment to measure serum concentrations of PAPP-A and fβ-hCG and to all use the same risk estimation software. Subsequently, they all decided to participate in the UK-NEQAS quality assurance programme for the first trimester combined test and to initiate a Dutch programme for quality assurance as well. They also agreed on mutual and regular evaluation of their UK-NEQAS results. Moreover, they annually evaluate the settings of their risk estimation software.

In this report, written on behalf of all screening laboratories and by assignment of the RIVM Centre for Population Research, the performance indicators related to the quality of the analysis of PAPP-A and fβ hCG for all laboratories is presented, as is the evaluation of the settings and performance of the risk calculation software. This is the first report to do so. Data collection for some of the laboratories already started at the beginning of the programme and where available and relevant, data from 2007 and 2008 are also presented (also to account for the quality of the combined test in 2007 and 2008). This report aggregates data adapted from the annual reports of the individual laboratories. Additional data concerning the performance of the Down's screening laboratories has already been published in three RIVM reports (5-7).

2 Materials and Methods

For the performance of the test, all laboratories complied with the guidelines issued by the director of the programme, the Centre for Population research and assembled by the Central Agency.[1] In general, blood sampling was done between a gestational age (GA) of 8 and 14 weeks and the nuchal translucency (NT) measurement carried out at a crown-rump-length (CRL) of 45-84 mm.

All Dutch screening laboratories used Lifecycle 2.2 risk estimation software, in combination with Elipse Configuration Tool 2.1 (PerkinElmer Life sciences, Turku, Finland). The parameters in Elipse are virtually the same for all laboratories and are available online.[2]

The Dutch screening laboratories were asked to fill out an Excel sheet with relevant data to evaluate the performance of the combined test and send this to the representative of the reference laboratory (RIVM). A template of the Excel sheet is presented in Annex 3.
These data were analysed to identify regional differences in the screened population and in the execution of the test. Moreover, data were used to review the performance indicators of the combined test. For part of that work, the software programme "QA tools" was used (version 1.0; MediaInnovations, Leeds, UK)
All laboratories participated in the UK-NEQAS first trimester combined test quality assurance scheme. The collective data of the seven laboratories were reported on a monthly basis and these reports are crafted into evaluation reports that are discussed in the regular meetings of the group of screening laboratories. One of these (also available on http://www.rivm.nl/downlab) is attached as Annex 1 to this report.
Finally, in October 2009 a survey was carried out to investigate whether the risk estimation software of the laboratories contained the correct settings. Based on fixed demographic data and fixed experimental results, a calculation of MoMs and risks was requested from all laboratories. In Annex 2, an analysis of this data is presented.

The screening laboratories are:

Reference laboratory Down's Syndrome screening, RIVM, Bilthoven (RIVM),	Utrecht and Leiden region (SPSRU and RCPS-NZH;
Clinical Chemical laboratory, Free University Medical Centre, Amsterdam (VUMC)	Amsterdam region (RCPS)
Clinical Chemical laboratory, Amsterdam University Medical Centre, Amsterdam (AMC)	Amsterdam region (SPSAO)
Clinical Chemical Laboratory, Groningen University Medical Centre, Groningen (UMCG)	Northern region (SPSNN)

[1] http://rivm.nl/Bibliotheek/Professioneel_Praktisch/Richtlijnen/Preventie_Ziekte_Zorg/Algemene_kwaliteitseisen_voor_laboratoria

[2] http://www.rivm.nl/downlab/Images/instellingen_LC_19052008_tcm30-38017.pdf

Clinical Chemical laboratory, Alysis Zorggroep, Arnhem (Rijnstate)	Nijmegen and Tilburg region (SPN),
StAR, Medical Diagnostic Centre, Capelle a/d Ijssel (StAR)	Rotterdam region (SPSZN);
Clinical Chemical Laboratory, Maastricht University Medical Centre, Maastricht (MUMC)	Southern region (RSPSM);

3 Results

3.1 Number of tests performed, gestational age, maternal age.

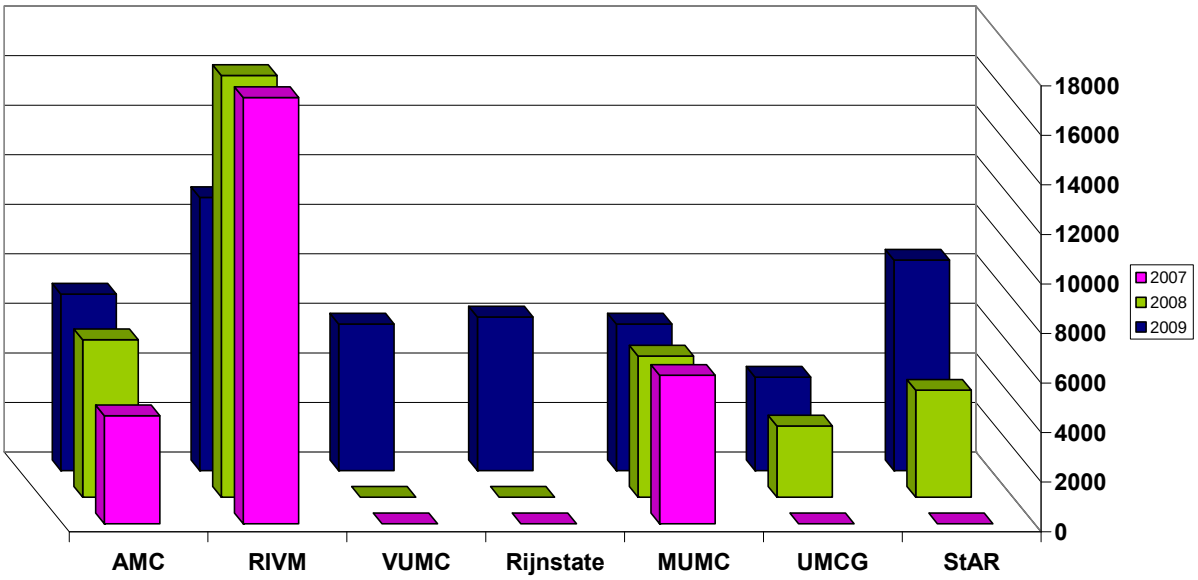

Figure 1 Number of samples analysed by the screening laboratories between 2007 and 2009. Note: data were not provided or available for all years.

In Figure 1, the total number of samples submitted to the first trimester combined tests of all the laboratories is given. This number for 2009 was 48,457 (representing a 25.7% uptake, based on a birth rate of 18,4915 live-borns for 2009 (www.cbs.nl, 10.01.2011) and a 2% correction for lost pregnancies). Of which 1.3% were obtained from women with a twin pregnancy (range for the laboratories: 0 – 3.1%). In addition 0.32% (0 – 0.9%) were samples from women with a previous DS pregnancy.

In Figure 2, the maternal age for 2009 is represented.
While in general there is not much difference in median maternal age at testing between 2007-2009, there are some differences between the median ages of the populations of the various laboratories. Especially those of the MUMC and StAR are notably lower.

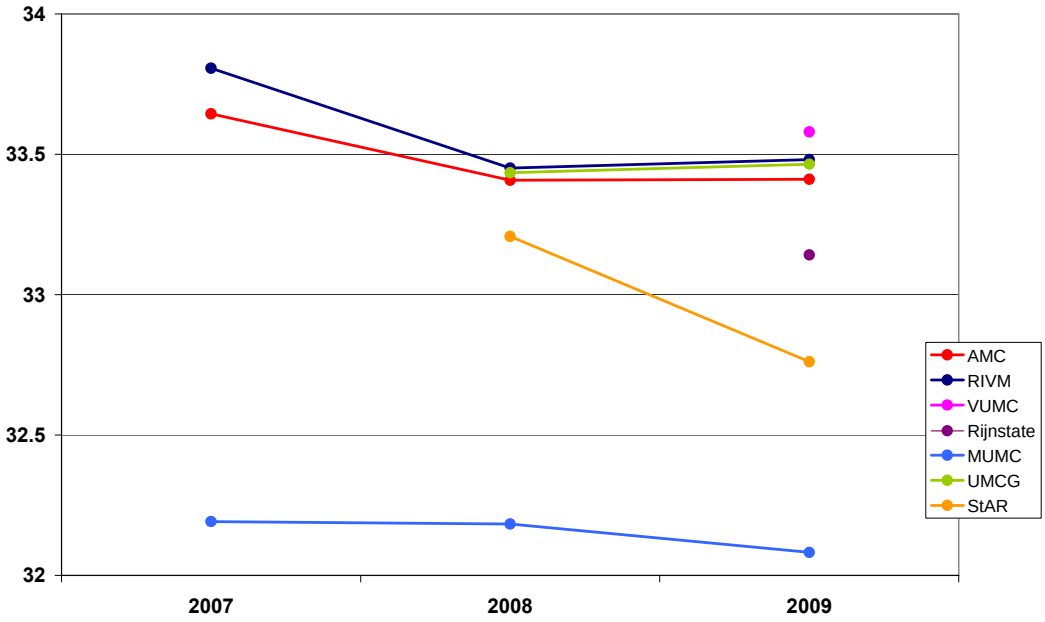

Figure 2 Median maternal age (at the moment of the test) of women requesting a combined test.

In Figure 3, the distribution of GA at blood sampling for the various laboratories is presented. It appears that there are notable differences between the practices of the regions. In the regions of StAR, UMCG and AMC samples were taken quite early GA (around 10 weeks), while the distribution is more even for VUMC, RIVM and Rijnstate. The MUMC collects the samples comparatively late.
Figure 4 gives an overview for the GA of the tested women as recorded by four laboratories for 2007-2009. While this distribution was stable for the regions of the laboratories of the RIVM (rather late in the first trimester and tending to be later), UMCG (early) and MUMC (late), there was a marked change between 2008 and 2009 for the AMC (early in first trimester).

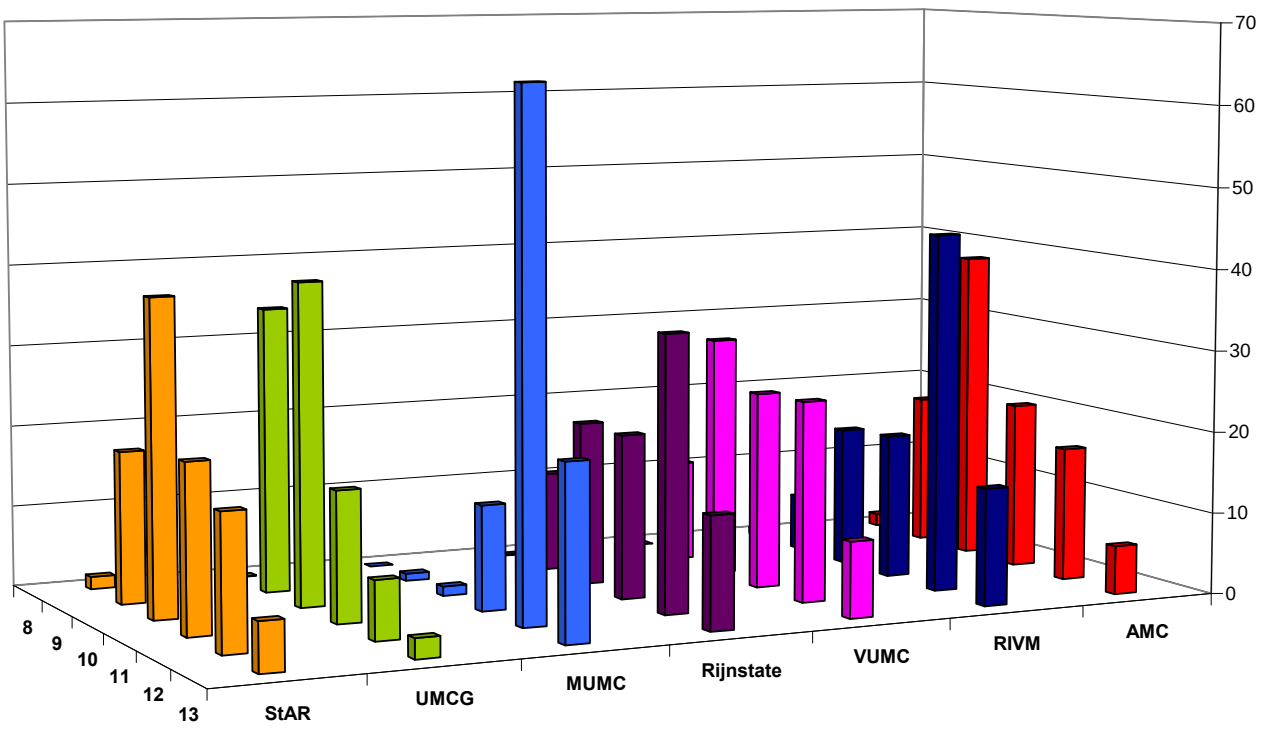

Figure 3: Distribution of GA at blood sampling (2009).

In the Netherlands, the final, combined risk is either calculated in the screening laboratory based on LifeCycle-Elipse software or, alternatively, in a general hospital or centre for echoscopy, using the FMF/Astraia software. The latter are not reported back to the laboratories. Thus, from the StAR and UMCG laboratories, no combined risks are available. In the regions of the VUMC and MUMC, risks are calculated exclusively by the laboratories. Finally, 85% 55% and 15% of the risks of the RIVM, Rijnstate and AMC laboratories respectively, is calculated in the laboratory. Thus, only for the latter five laboratories, can a relationship between maternal age and the percentage of high risk results be given (Figure 5).

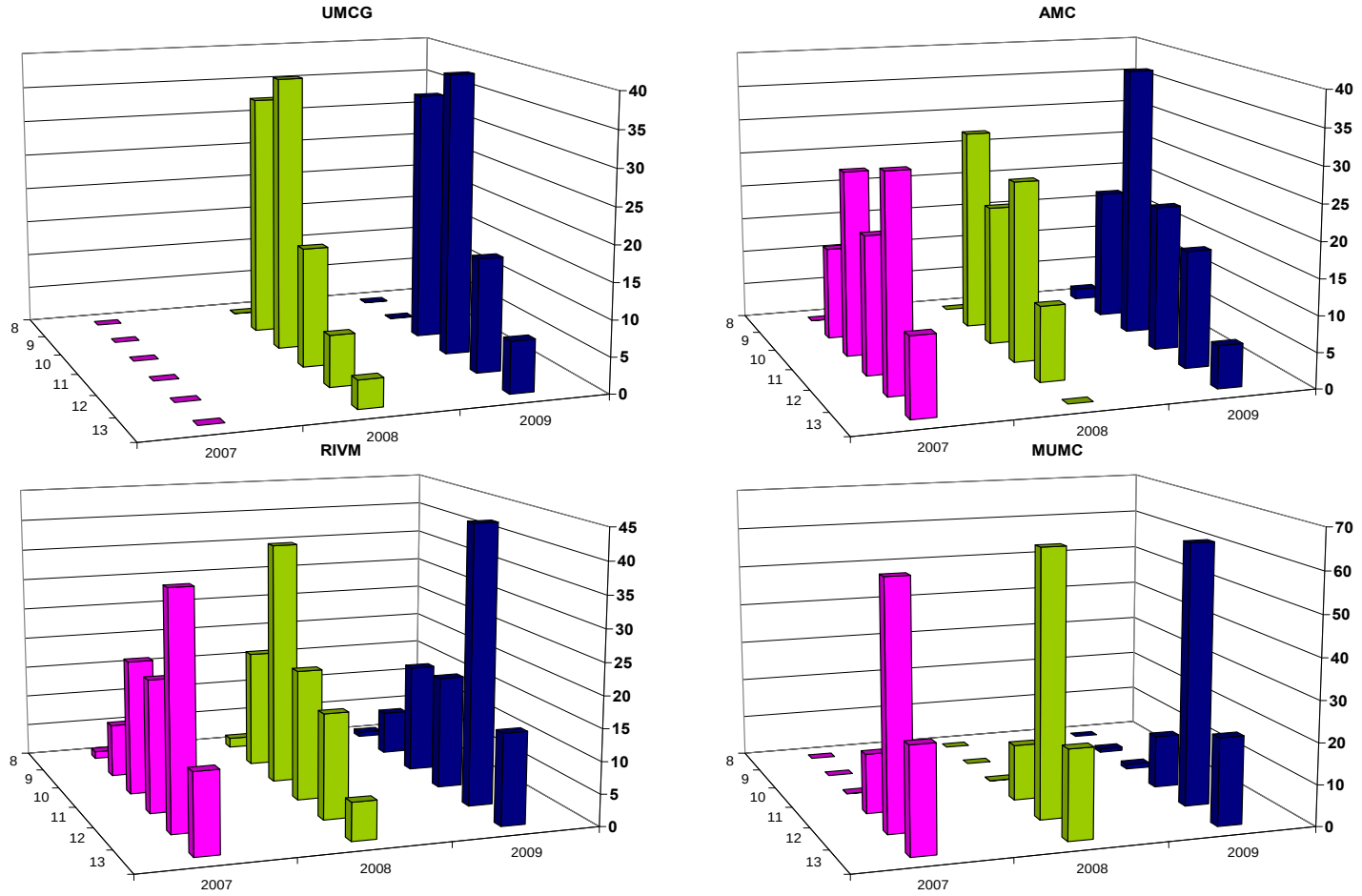

Figure 4: Distribution of GA at blood sampling for the laboratories of the UMCG, AMC, RIVM and MUMC, for 2007, 2008 and 2009.

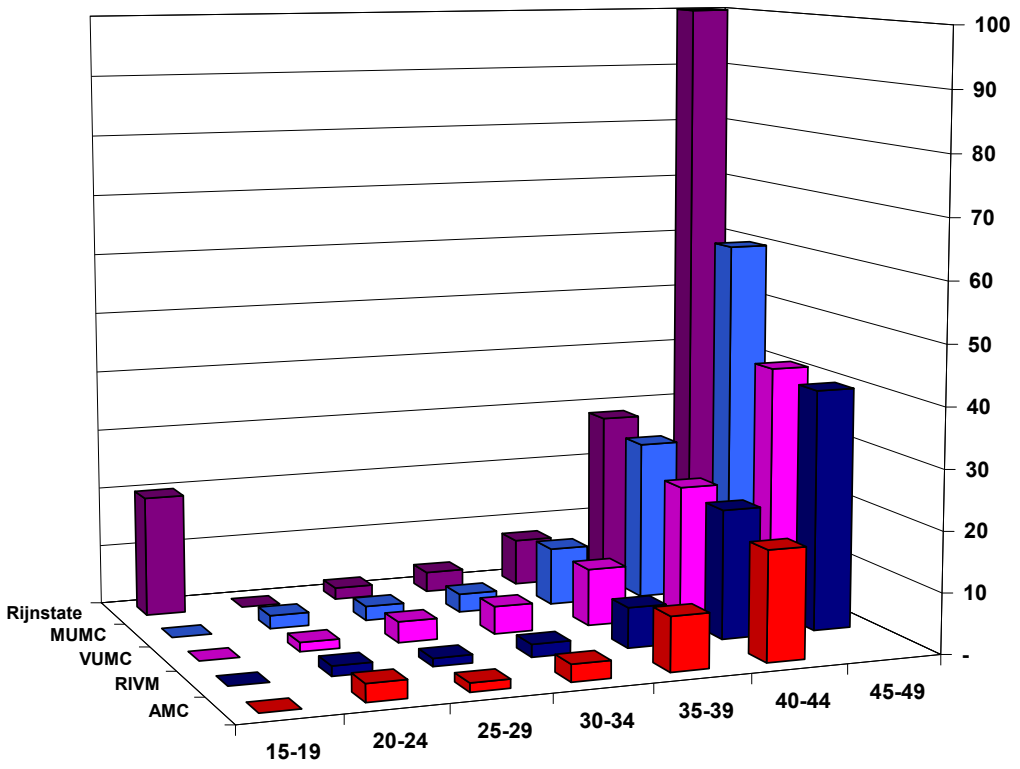

Figure 5: Percentage of high-risk results for laboratories in which combined risks are calculated.

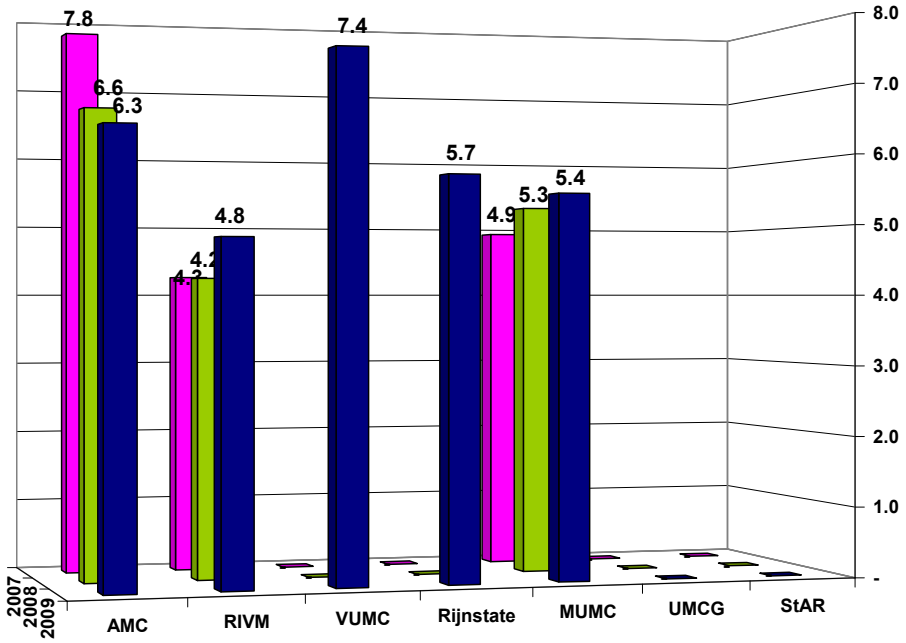

Figure 6: Overall percentage of high-risk results for laboratories in which combined risks are calculated (2007-2009).

In Figure 6 the percentage of high risks for 2007-2009 is presented for those laboratories for which data is available. Apparently, the percentages of high-risk results of the RIVM are rather low, while those of the AMC and UMCG are rather high.

3.2 Evaluation of laboratory parameters.

For a risk calculation process to function properly, a number of demands need to be met. Thus, the concentrations of PAPP-A and fβ-hCG need to respectively increase and decrease with GA, and to the amount as defined by the settings for this in the risk estimation software. Concentrations are converted to MoM values that relate to the maternal weight. Again, this relationship is precisely defined in the software and the data of the laboratories should match this definition. Finally, monthly median MoMs of normal pregnancies should be about 1.0 and the log MoM should fit a Gaussian distribution. An evaluation of all these parameters is given below.

PAPP-A and fbeta concentrations in relation to GA.
In Figures 7 and 8 the median concentrations of PAPP-A and fβ-hCG are depicted for all laboratories for which data was available. Notably, between 2007 and 2009 the graphs representing the concentrations for a given GA tend to differ less and fit the median concentration as defined in the software more closely. In 2008, the results of the AMC for both PAPP-A and fβ-hCG seem to deviate a little but this was not seen in 2009. There is no obvious explanation for this.

PAPP-A and fβ hCG monthly median MoM 2007-2009
Data on the monthly medians are presented in Figure 9. The data show that monthly medians in general are between 0.9 and 1.1 (an arbitrary but generally accepted range). However, there are some periods in which, especially for PAPP-A, there was some fluctuation. Especially the data from the laboratories of StAR,

VUMc and AMC showed lower PAPP-A MoM early in 2009 (due to a manufacturing error in the experimental PAPP-A kits). Data from laboratories with a relatively low throughput should have a higher variation in monthly median MoMs. This seems true in particular for the results of the UMCG. In general however, the results of Figure 9 do not indicate any temporary or permanent deviations from 1.0, other than the one mentioned above.

PAPP-A and fβ hCG and correction for maternal weight.
Figure 10 presents the relationship between MoM and maternal weight. There is some scatter of the data at low and high maternal weights due to the low number of samples but basically, the relationship is the same for all laboratories for both PAPP-A and fβ hCG, and closely matches the curve indicating the weight correction equation as set in the LifeCycle Elipse software of the RIVM. Data for 2007 and 2008 are not complete but not different from the data of 2009, with the exception of the relationship between maternal weights and PAPP-A for the RIVM in 2007.

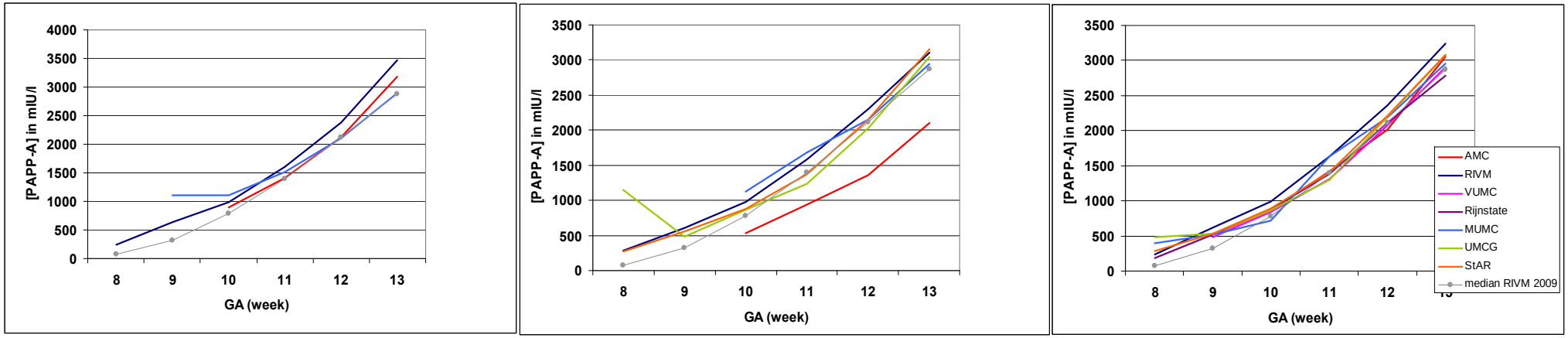

Figure 7: Median serum concentration PAPP-A for GA (weeks). As a reference in grey, the median concentration as defined in the software of the RIVM (2009) is plotted.

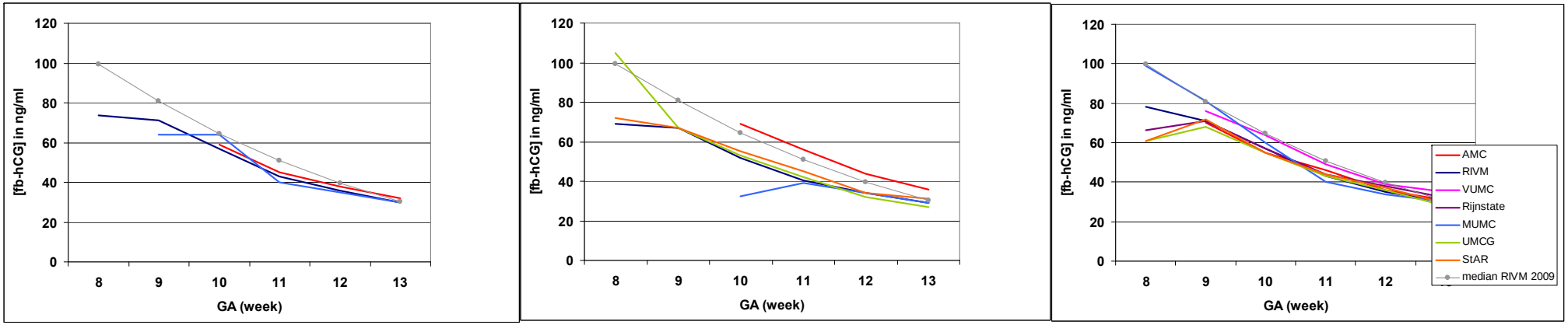

Figure 8: Median serum concentration f b hCG for GA (weeks). As a reference in grey, the median concentration as defined in the software of the RIVM (2009) is plotted.

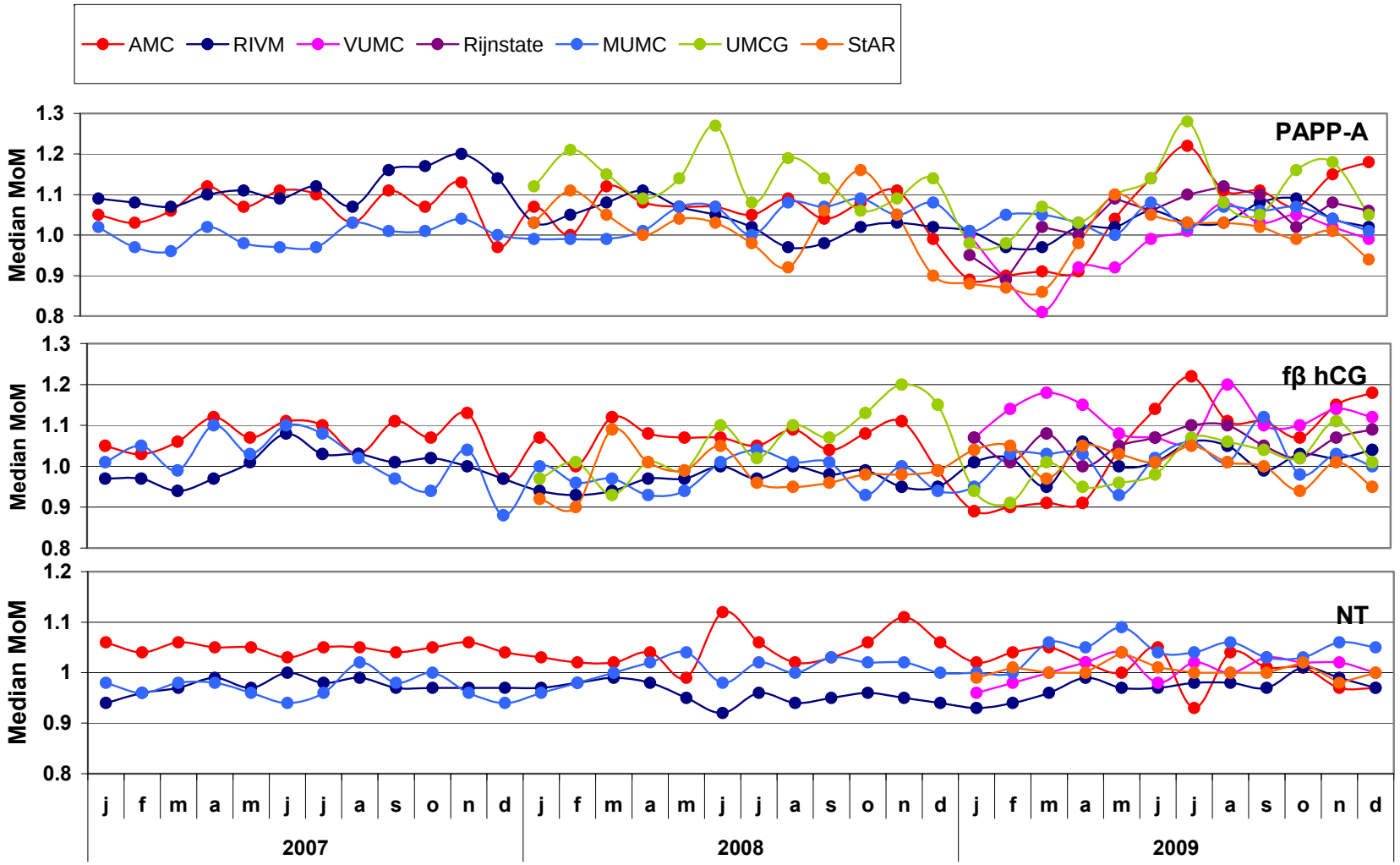

Figure 9: Monthly (weight-corrected) medians (PAPP-A, fβ hCG and NT) of the Down's screening laboratories 2007-2009.

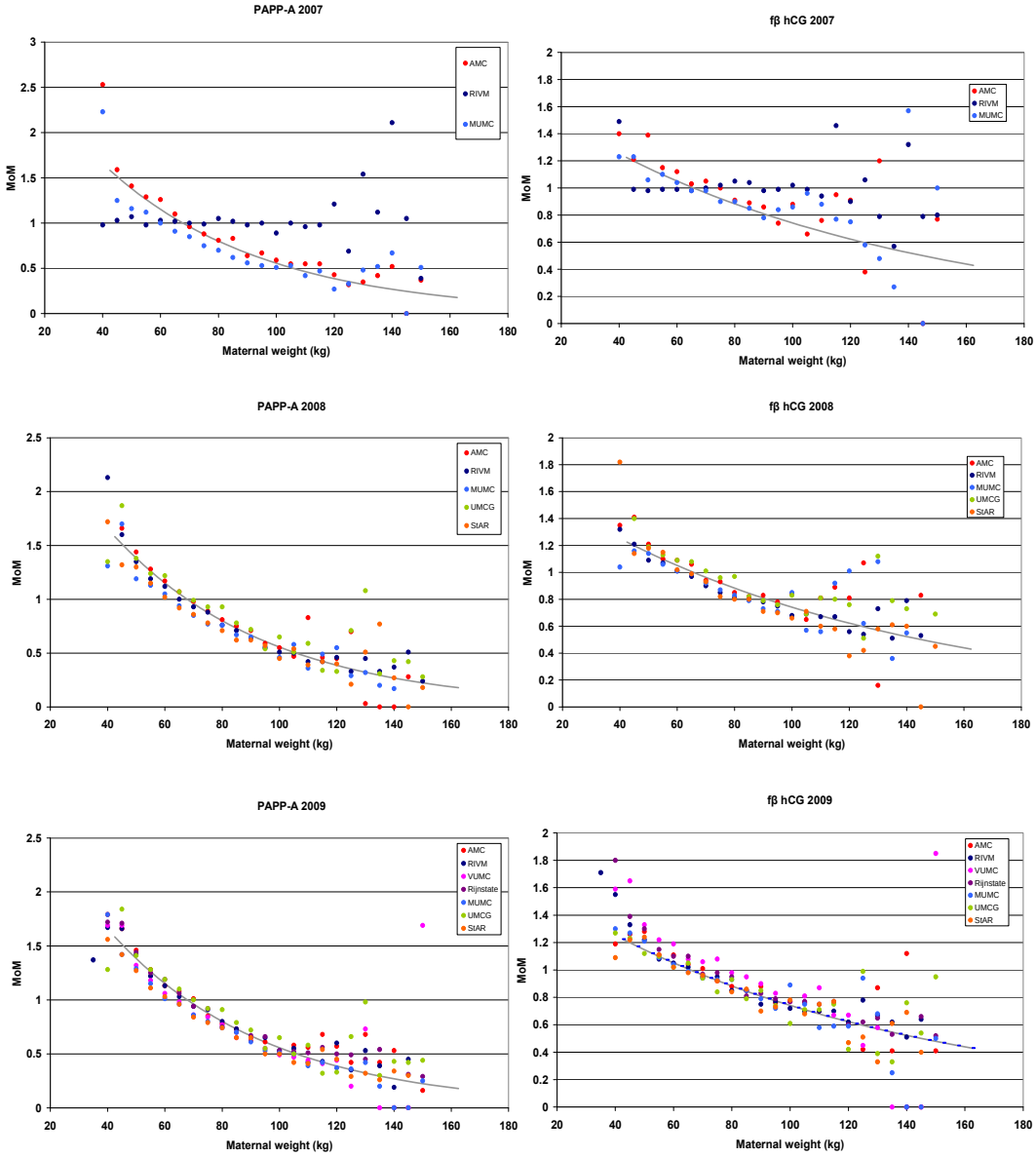

Figure 10: Relationship between maternal weight and median MoM PAPP-A and fβ hCG.

To investigate whether the distributions of the log MoM PAPP-A and log MoM fβ hCG were Gaussian (a prerequisite when using the risk estimation software), the percentiles of the log MoM on a Z-scale should produce a linear regression line through (0.0). For all parameters and for 2007, 2008 and 2009, this appeared to be the case (data not shown). To compare the distributions of the laboratories, the approximations of the linear regressions are given (Figure 11). The data show that the distributions for PAPP-A, fβ hCG and NT for all laboratories were quite comparable. Some deviations, in accordance with those (e.g., for the

weight corrected PAPP-A MoM) described previously, were seen in the graphs for 2007 and 2008 (data not shown).

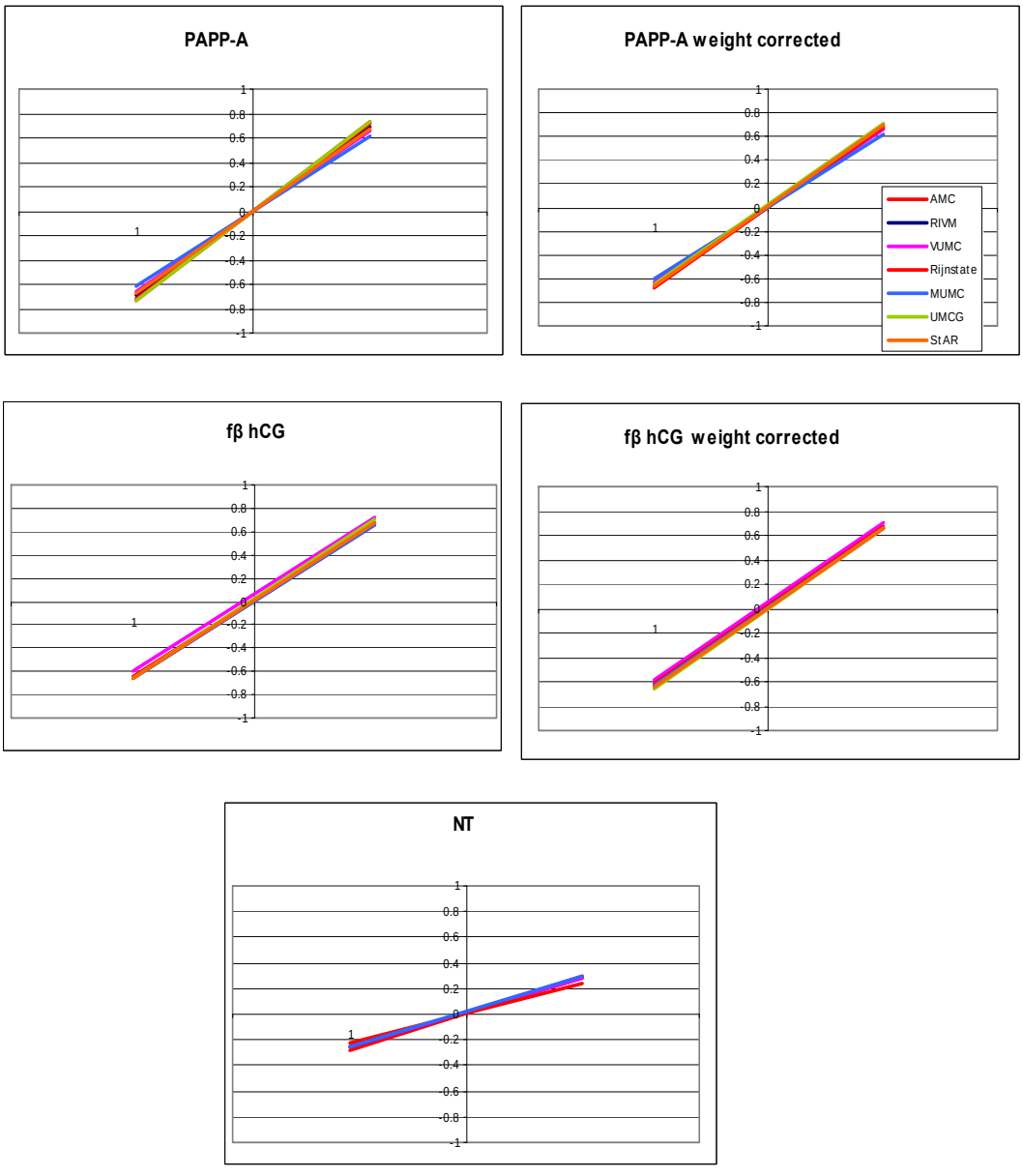

Figure 11: Normal distribution of the PAPP-A, fβ hCG and NT MoM (weight corrected and not weight-corrected) for the Dutch screening laboratories (2009).

In Table 1 the correlation coefficients between PAPP-A and fβ-hCG are given. These should match those set in the risk calculation software. The results in the table show that there are some differences between the coefficients but that in

general, they are similar (the UK National screening committee, as a reference, suggested this correlation coefficient to be between 0.05 and 0.025[3])

Table 1: Correlation coefficients between PAPP-A and fβ hCG in singleton pregnancies for 2007-2009.

	2007		*2008*		*2009*	
	Log-not weight_corr	Log_weight corrected	Log-not weight_corr	Log_weight corrected	Log-not weight_corr	Log_weight corrected
AMC	0.290	0.248	0.278	0.236	0.297	0.249
RIVM	0.255	0.193	0.270	0.217	0.268	0.216
VUMC					0.293	0.239
Rijnstate					0.296	0.228
MUMC	0.255	0.209	0.261	0.209	0.259	0.208
UMCG			0.281	0.232	0.291	0.233
StAR			0.263	0.196	0.295	0.242

[3] National Down's syndrome screening programme for England-National Specification for Risk Calculation Software and Guidance on implication. October 2004.

4 Discussion

This report is the first one in an annual series on the performance of the Dutch Down's screening laboratories. It is an aggregation of relevant data reported by the laboratories themselves and data reported by the UK NEQAS organisation for quality assurance (Edinburgh, UK). The aim of these reports is to account for the quality of the first trimester combined test and adaptation to the test as a consequence of the ongoing process of quality assurance.

Data on the total number of screening samples show that there is a slight rise in 2009, as compared to 2008 (Figure 1). Figure 2 shows that there is some variation in maternal age at sampling.
As can be seen from Figures 3 and 4, the GA at which the blood sampling for the first trimester is done varies, sampling in some regions being quite early in the first trimester (AMC, UMCG) and in others quite late (MUMC). In light of recent data in the literature (8, 9), blood sampling early in the first trimester combined with an NT measurement late in the first trimester seems favourable for the performance of the risk estimation. Whether this applies to the Dutch situation remains to be seen. A thorough analysis of the performance of the test in terms of detection rate (DR) and the odds of being affected given a positive result (OAPR) needs to be performed. Those data are currently not available. Besides, the logistics of blood sampling and NT measurement is sometimes chosen to facilitate swift processing from application to result. It needs to be kept in mind that an adaptation of the logistics cycle will sometimes demand an effort from the participants to become acquainted with the new routine.

With respect to the percentage of high-risk results rate (SPR) of the screening laboratories (Figures 5 and 6) for the VUMC this is notably high, while it is low for the RIVM. It is noteworthy that the UK-NEQAS data for these laboratories (Annex 1) are in line with this. In the virtual risk calculations of Annex 2, a similar pattern is seen. As the VUMC 'biochemistry-only' risks are inconspicuous, it seems that especially the NT median as applied by the VUMC may be of significance in this. Indeed, the NT MoM of the VUMC are different from those of the other laboratories. The VUMC applies a different NT MoM equation, as discussed and acknowledged by the other screening laboratories. The SPR of the 45-49 year age group (Figure 5) is not reliable, due to the low number of pregnancies in these groups.

Data on the total number of screening tests show that there is a slight rise in the numbers of 2009, as compared to 2008 (Figure 1).

In Figures 7 and 8 the relationship between concentrations and GA is given, as compared to the relationship defined in the risk estimation software. Especially in 2009, the relationships for all the laboratories fitted the defined medians closely, indicating, in combination with all available data, that the current definition is correct and adjustment is currently not indicated.

The monthly median (weight-corrected) MoM (Figure 9) shows that, with the exception of early in 2009, the MoM were rather stable. The variation in the data is an illustration of what the natural variation in MoM may be at any given moment. The temporary decrease in PAPP-A MoM early in 2009 appeared to be caused by a flaw in the production of PAPP-A kits for the DelfiaXpress (as used

in the laboratories of VUmc, StAR and Rijnstate). After the correction of this error by the manufacturer, the PAPP-A MoM returned to normal. This can also be seen in the figures on PAPP-A MoM of the UK-NEQAS report of Annex 1. The figures on the calculated risks in the UK-NEQAS report appeared to be quite stable, indicating that the influence of this production error was rather small. However, the consequences of erroneous low PAPP-A and thereby an increased biochemical risk calculation appeared to be considerable, leading to an increase of 30% in unjustified invasive diagnostic testing. No miscarriages were caused due to these invasive procedures (Report Erasmus University Rotterdam, Dr Y. de Rijke).

The relationship between the maternal weights and the MoM were generally in accordance with the equations as implemented in the software, except for the weight-corrected MoM of PAPP-A and fβ hCG for the RIVM in 2007. The underlying problem appeared to be an erroneous weight correction equation and this was corrected in May 2008. The sequence of discovery, evaluation and the ultimate calculation of a new weight correction equation is documented in an internal laboratory report.

With respect to the distributions of the various parameters, it can be concluded that the log MoM were distributed normally and that the mean log MoM approached 0.0 (equal to a median MoM of 1.0) (Figure 11). The correlation coefficients differed to some extent among the laboratories. As soon as international standards for the parameters of the risk calculation are available (the NHS has published some; National specification for software and guidance on implementation (2004), these and other settings of the software will be compared to these standards.

As can be concluded from the data in Annex 2, the results of the risk calculation software divide the laboratories in two consensus groups; for two laboratories there is no consensus. While in the past laboratories were allowed to deviate from the consensus settings to solve very specific regional problems concerning the risk calculation, which explains the laboratories of the UMCG and VUMC being out of consensus, it should be investigated whether in the future the risk calculations may be re-harmonised. Notably, the divide is not exclusively between users of the DelfiaXpress and Delfia users and the differences in the ultimate risk calculations are small.

5 Conclusions and Recommendations

In general, the elements of the QA architecture currently in place and the practice and experience of the past three years have produced a sensitive tool to identify errors in the analysis and risk calculation process in a timely manner. Moreover, the annual evaluation identifies areas for improvement.
For 2010, attention will focus especially on the identification of the small but significant differences in risk calculations among the laboratories. Moreover, the analyses of the Dutch system of quality control cycles will be incorporated into the QA architecture.
Finally, in a few years, when the 'Peridos' database is filled with the outcomes of pregnancies, regional DR will also be reported and aspects of the screening of the best performing regions will be adopted nationwide to improve the performance of the entire screening programme.

6 References

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3 Position of the Dutch government concerning the report Prenatal screening (2) of the Dutch Health Council-Letter to the parliament of the state secretary for Health, Welfare, and Sports, September 15, 2005 (In Dutch).

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8 Kirkegaard I, Petersen OB, Uldbjerg N, Tørring N. Improved performance of first-trimester combined screening for trisomy 21 with the double test taken before a gestational age of 10 weeks. Prenat Diagn. 2008 Sep;28(9):839-44

9 Kuc S, Koster MP, Visser GH, Schielen PC. Performance of first-trimester serum screening for trisomy 21 before and from 11 + 0 weeks of gestational age in the Netherlands. Prenat Diagn. 2010 Sep;30(9):906-8.

Annex 1 UKNEQAS report on Down's syndrome screening laboratories, cycle 139

As mentioned in the 'Introduction' the Dutch screening laboratories all participate in the UKNEQAS quality assurance programme for the first trimester Down's syndrome screening. Of the combined results, a monthly summary report is assembled and published on the web site of the reference laboratory, for the reference of the participating laboratories. In this annex a sample of such a report is presented. Please note that demonstrating high or low values in this overview is by no means related to the performance of the laboratory –only after ranges of correctness are given (to be established) do the data become meaningful. Possibly, all the laboratories are within these limits.

UKNEQAS report on Down's syndrome screening laboratories

Cycle no 139

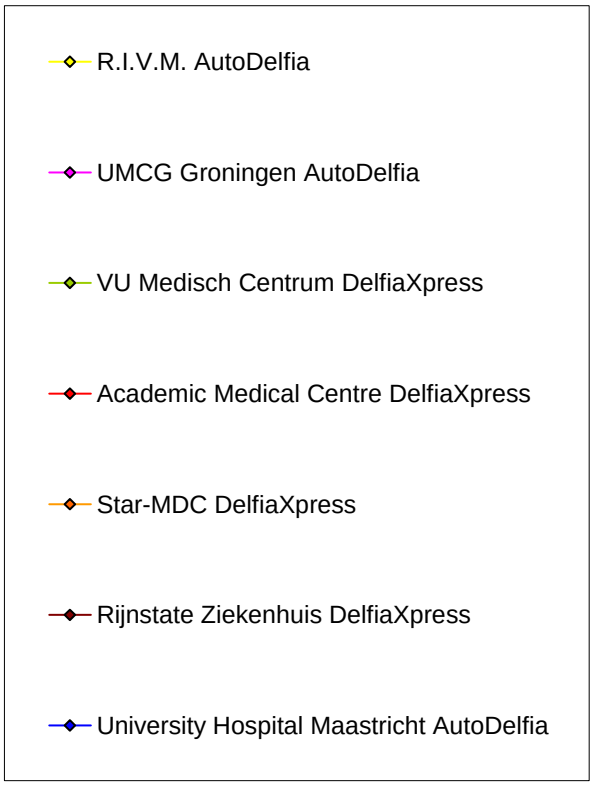
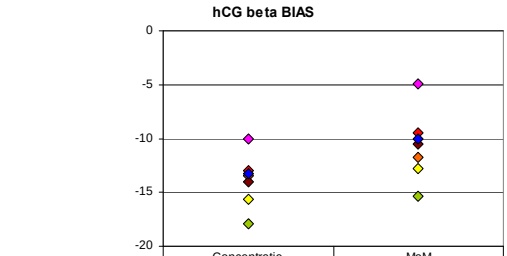
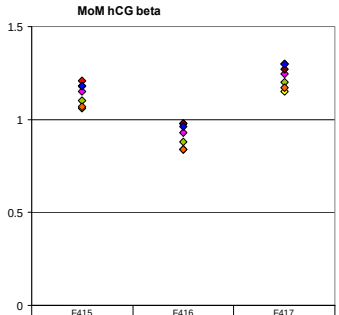


Figure 1: Concentration and MoM fβ hCG and PAPP-A.

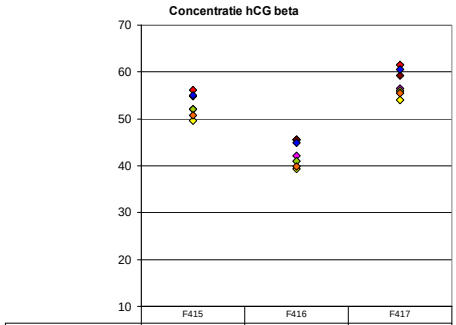


	Concentratie	MoM
R.I.V.M. Distribution 139	-15.6	-12.8
UMCG	-10	-4.9
VU Medisch Centrum	-17.9	-15.4
Academic Medical Centre	-13	-9.5
Star-MDC	-13.5	-11.8
Rijnstate Ziekenhuis	-14	-10.5
University Hospital Maastricht	-13.3	-10

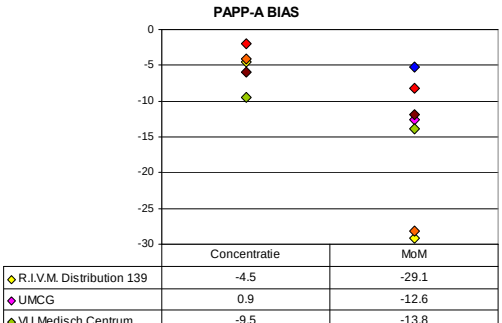


	F415	F416	F417
R.I.V.M. Distribution 139	1.06	0.84	1.15
UMCG	1.15	0.929	1.247
VU Medisch Centrum	1.1	0.88	1.2
Academic Medical Centre	1.21	0.98	1.3
Star-MDC	1.07	0.84	1.17
Rijnstate Ziekenhuis	1.18	0.98	1.27
University Hospital Maastricht	1.18	0.96	1.3

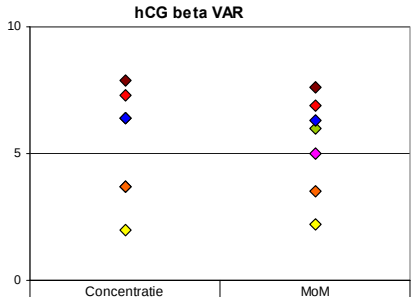
Figure 2 BIAS and VAR Concentration and MoM fβ hCG and PAPP-A.



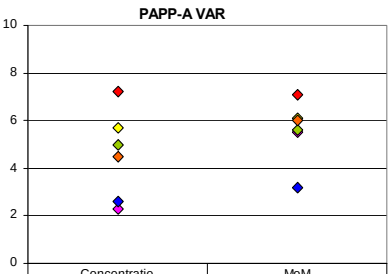
	F415	F416	F417
R.I.V.M. Distribution 139	49.7	39.3	54
UMCG	52.1	42.1	56.5
VU Medisch Centrum	52	41	56
Academic Medical Centre	56.2	45.6	61.6
Star-MDC	50.78	39.9	55.49
Rijnstate Ziekenhuis	54.8	45.53	59.22
University Hospital Maastricht	55.07	44.81	60.53



	Concentratie	MoM
R.I.V.M. Distribution 139	-4.5	-29.1
UMCG	0.9	-12.6
VU Medisch Centrum	-9.5	-13.8
Academic Medical Centre	-2	-8.2
Star-MDC	-4.1	-28.2
Rijnstate Ziekenhuis	-6	-11.9
University Hospital Maastricht	0.8	-5.3

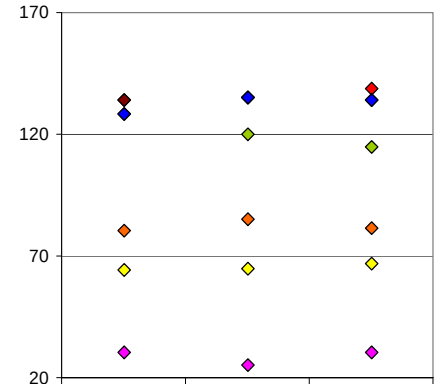


	Concentratie	MoM
R.I.V.M. Distribution 139	2	2.2
UMCG	3.7	5
VU Medisch Centrum	6.4	6
Academic Medical Centre	7.3	6.9
Star-MDC	3.7	3.5
Rijnstate Ziekenhuis	7.9	7.6
University Hospital Maastricht	6.4	6.3



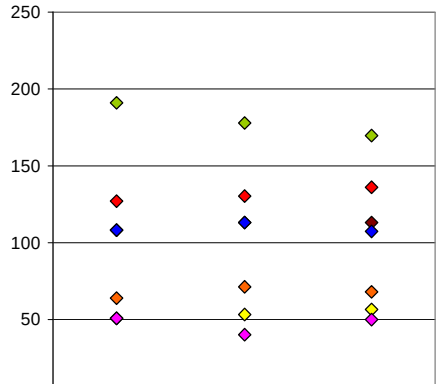
	Concentratie	MoM
R.I.V.M. Distribution 139	5.7	6.1
UMCG	2.3	5.5
VU Medisch Centrum	5	5.6
Academic Medical Centre	7.2	7.1
Star-MDC	4.5	6
Rijnstate Ziekenhuis	11.7	11.8
University Hospital Maastricht	2.6	3.2

Risico geen NT percentage van gemiddelde NL labs



	F415	F416	F417
R.I.V.M. Distribution 139	64	65	67
UMCG	31	25	31
VU Medisch Centrum	129	120	115
Academic Medical Centre	134	135	139
Star-MDC	80	85	81
Rijnstate Ziekenhuis	134	135	134
University Hospital Maastricht	129	135	134

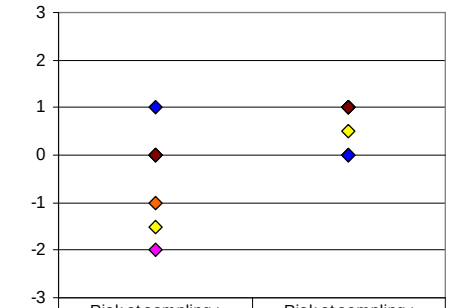
Risico NT gecomb percentage gemiddelde NL labs



	F415	F416	F417
R.I.V.M. Distribution 139	51	53	57
UMCG	51	40	50
VU Medisch Centrum	191	178	170
Academic Medical Centre	127	131	136
Star-MDC	64	71	68
Rijnstate Ziekenhuis	108	113	113
University Hospital Maastricht	108	113	107

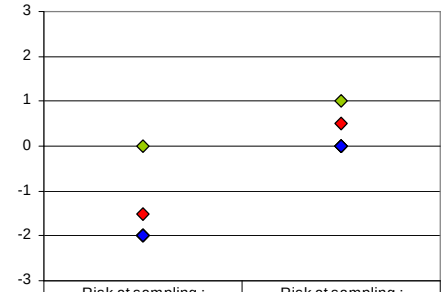
Figure 4. BIAS and VAR of risks.

'Running Risk Score'



	Risk at sampling : Biochemistry only	Risk at sampling : Biochemistry only
R.I.V.M. 139	-1.5	0.5
UMCG	-2	0
VU Medisch Centrum	0	1
Academic Medical Centre	0	1
Star-MDC	-1	1
Rijnstate Ziekenhuis	0	1
University Hospital Maastricht	1	0

SD of 'running risk score'



	Risk at sampling : Biochemistry + NT	Risk at sampling : Biochemistry + NT
R.I.V.M. 139	-2	0
UMCG	-2	0
VU Medisch Centrum	0	1
Academic Medical Centre	-1.5	0.5
Star-MDC	-2	0
Rijnstate Ziekenhuis	-2	0
University Hospital Maastricht	-2	0

Figure 5. Trend of BIAS and VAR of PAPP-A and fβ hCG in time.

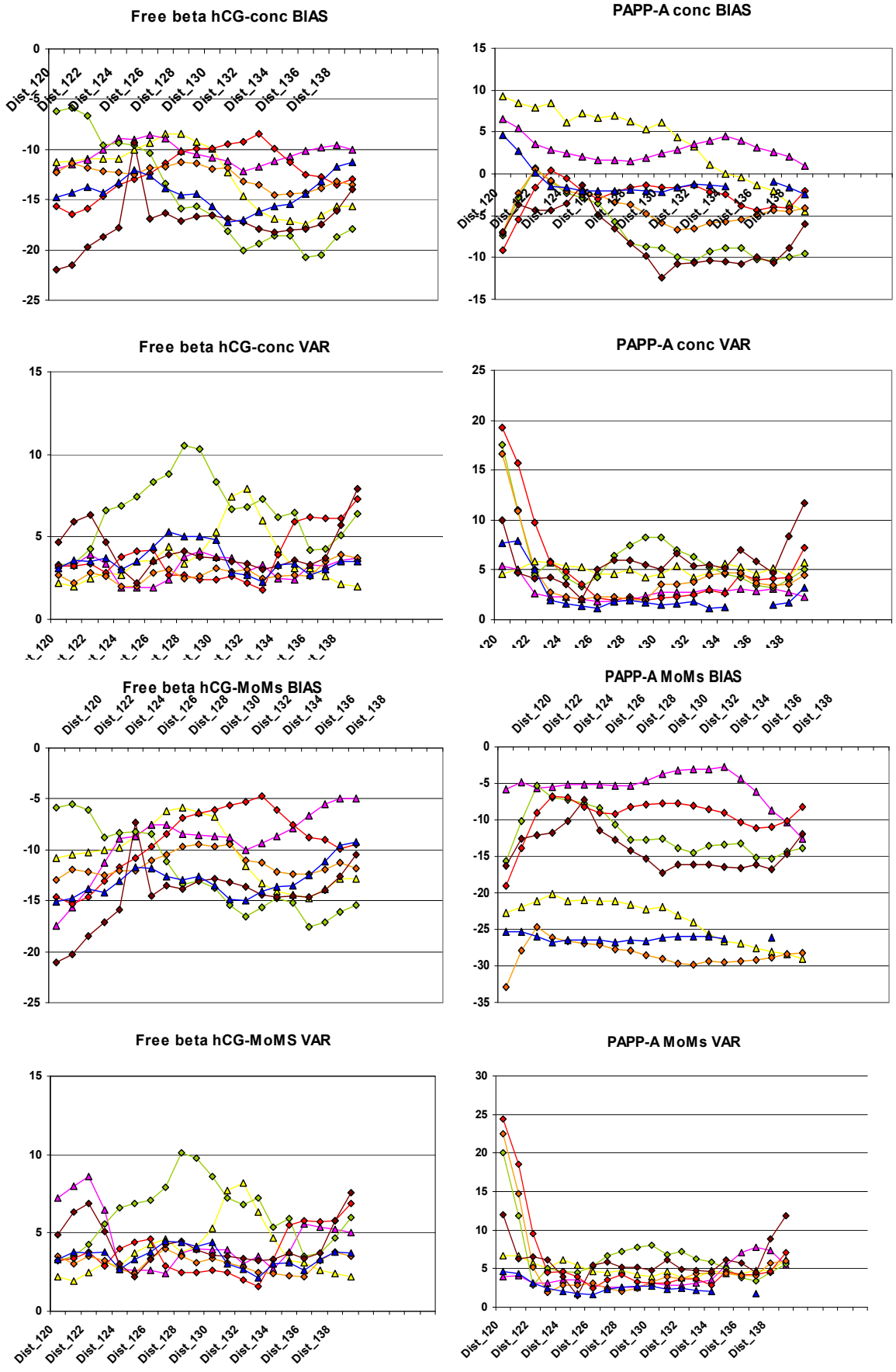
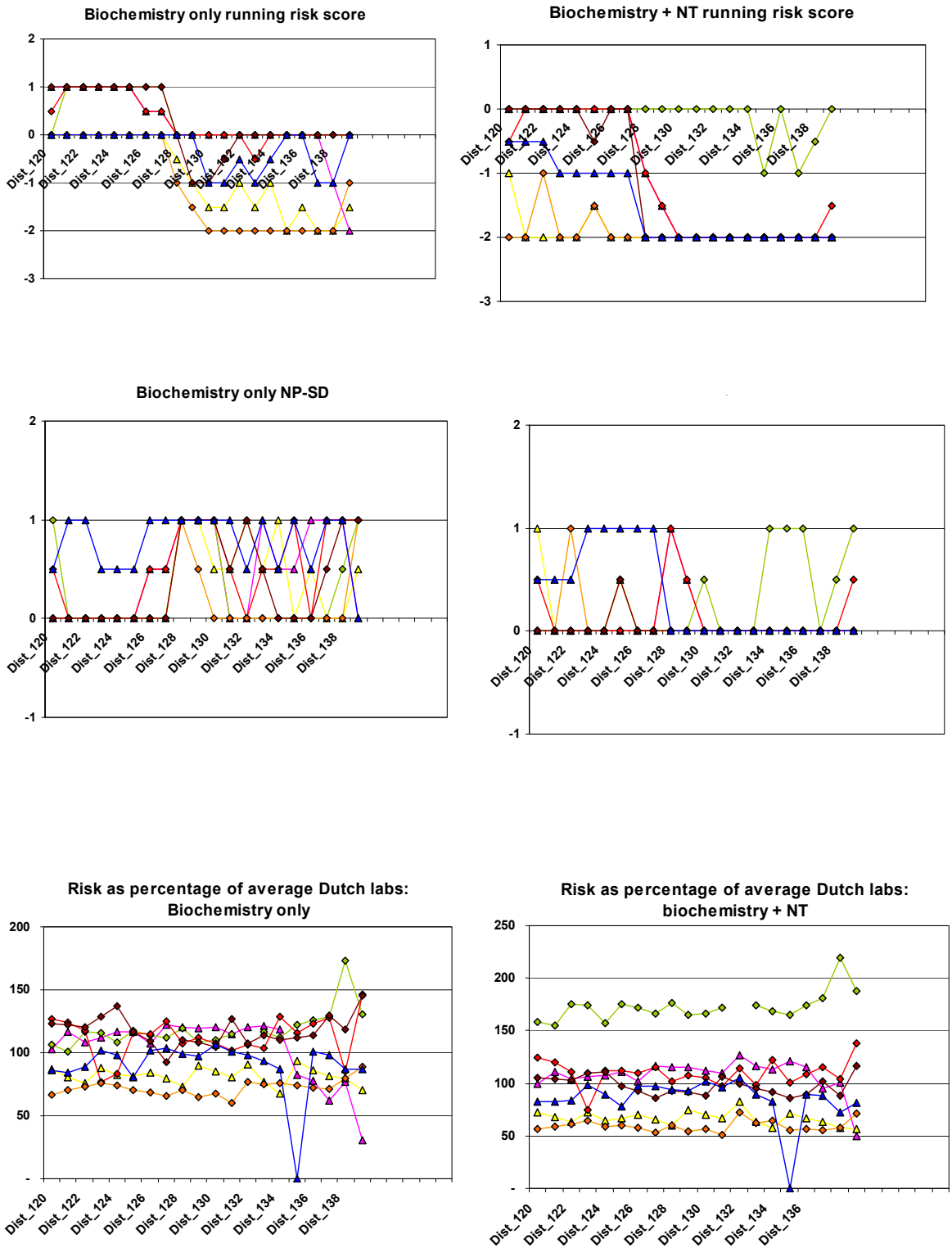


Figure 6. Trend of risks in time.



Annex 2 Summary of risk calculations of the Dutch screening laboratories for five test pregnancies

Within the policy of the Dutch screening programme we aim to harmonise the risk calculations as closely as possible. Thus, the screening laboratories work with the same software and use the same settings. Nevertheless, based on discussions during meetings of the screening laboratories, adjustments were allowed to cover for various problems. Thus, one laboratory was allowed to work with a specific equation for the NT measurement, at the request of the sonographers in their region and some small differences in PAPP-A and fβ hCG median equations were allowed to correct for small analytical differences, due to the use of two different types of analysers (AutoDelfia and Delfia Xpress). Thus, in the laboratory of the UMCG different equations for PAPP-A and fβ-hCG medians and for the PAPP-A weight correction are applied and at the VUMC, a different equation for the NT median MoM is used.

Late in 2009, a survey was sent from the reference laboratory giving details of five imaginary pregnancies, with the request to report the MoMs (both uncorrected and weight-corrected), age risk, combined risk and the risk of an Edwards syndrome (trisomy 18) pregnancy using these data.

If the risk calculation software was installed equally in all laboratories, the calculated MoM and risks should exactly match. This, however was not the case. A summary of the analysis of all data of all laboratories is given in the table. Apparently, the laboratories can be divided in two consensus groups, producing almost identical risks. Concerning the ultimate risk calculation, the combined risks of the RIVM were among the lowest and those of the VUMc were among the highest (data not shown). Moreover, the NT MoM of the VUMC were higher than the NT MoM of all the other laboratories.

Parameter	Consensus group 1	Consensus group 2	Miscellaneous
NT MoM	**RIVM**, StAR, Rijnstate	UMCG, **MUMC,** AMC	VUMC
fbeta hCG MoM	RIVM, StAR, **MUMC**	Rijnstate, AMC, VUMC	UMCG
fbeta hCG MoM Corr	RIVM, StAR, **MUMC**	Rijnstate, AMC, VUMC	UMCG
PAPP-A MoM	RIVM, StAR, **MUMC,** AMC	Rijnstate, VUMC, **UMCG**	
PAPP-A MoM corrected	RIVM, StAR, **MUMC**	Rijnstate, AMC, VUMC	UMCG
Age risk	RIVM, StAR, **MUMC,** Rijnstate, **UMCG,** AMC, VUMC		StAR
DS Combined kans	No consensus		
Edwards combined kans	No consensus		

Note: In bold: Autodelfia platform, otherwise: DelfiaXpress platform.

Annex 3 Preliminary results of the SKML-QA programme.

In 2009, a Dutch QA programme was started, organised by the SKML (Stichting Kwaliteitsbewaking Medische Laboratoriumdiagnostiek). Summarised results of this programme are presented in the table

	PAPP-A		***fβ hCG***					
	2009		**2010**		**2009**		**2010**	
	Recovery	%CV	Recovery	%CV	Recovery	%CV	Recovery	%CV
AMC	91.1	2.9	85.7	3.2	93.3	3.3	97.9	3.4
AZM	97.4	3.3	94.0	3.8	96.0	2.6	95.5	2.2
StAR	93.0	2.4	86.3	3.7	95.1	2.5	97.8	3.7
Rijnstaete	95.7	4.4	90.0	3.2	96.6	3.3	99.1	4.3
RIVM	105.5	3.4	98.4	3.0	97.9	2.8	96.4	2.5
VUMC	92.6	3.1	85.2	3.8	99.1	4.1	95.6	3.5
UMCG	105.2	3.5	100.9	2.3	98.0	2.2	99.5	2.6

Results of the Dutch QA programme (SKML). Data are from about 60 measurements in 2009 and 40 measurements in 2010.

Annex 4 Headings of Excel sheet to report laboratory data to the reference laboratory

	Demographische gegevens										Gegevens
Laboratoriumcode	Datum aanmelden test	Geboortedatum	Eerdere DS zwangerschap	Diabetes zwangerschap	Bloedverlies	tweeling	NT	CRL	Datum_NT_meting	pr_weight	Zwangerschapsduur_bij_bloedafname	Concentratie PAPPA
1230637122	11-9-07	15-12-70	j	j	n	j	1.8	45	7-9-07	87	86	2830

	Demographics											Data risk estimation								Data outcome (optional)			
Laboratory code	Dat of test	DOB	Previous DS pregnancy	IDDM	Blood loss	Twin	NT	CRL	Date of NT	Weight	GA at bloos sampling	PAPP-A conc	MoM PAPPA	Wt corr MoM PAPPA	NT_MOM	fß hCG conc	MoM fß hCG	Wt corr MoM fß hCG	DS risk	Age risl=k	DOB	Sex	Birth weight	Aneuplody
1230637122	11-9-2007	15-12-1970	j	j	n	j	1.8	45	7-9-2007	87	86	2830	1.193	1.285	0.758	52.3	1.375	1.461	5300	470	18-03-2008	M	2350	geen

National Insitute for Public Health
and the Environment
P.O. Box 1 | 3720 BA Bilthoven
www.rivm.com