TNO report for
ZonMw

Comparison of introduction of three different strategies to prevent neonatal group B haemolytic streptococcal disease in the Netherlands

TNO innovation for life

June 1st, 2017

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Report for:	ZonMw
Date	June 1st, 2017
Authors	Dr. Suze M.P.J. Jans Dr. Marlies E.B. Rijnders
Projectnumber	060.19527
Reportnumber	R10650

Contact TNO	Suze Jans
Phone	+31(0)88 866 63100
E-mail	Suze.jans@tno.nl

Healthy Living
Schipholweg 77-89
2316 ZL LEIDEN
The Netherlands
POBox 3005
2301 DA LEIDEN
The Netherlands
www.tno.nl

T 31(0)88 866 61 00
infodesk@tno.nl

Abstract

Early onset Group B- haemolytic streptococcus infection (EOGBS) is an important cause of neonatal morbidity and mortality within the first week of life. Maternal colonization rates during pregnancy are estimated to be around 20% in the Netherlands. Around half of the children born from these mothers will become colonized and 1% will develop EOGBS. Primary prevention is possible by administrating antibiotics during labour (IAP). Different strategies are used to identify women in need of IAP. A cost effectiveness study showed a strategy with IAP treatment based on five risk factors (risk based strategy) or based on a positive screening test in combination with one or more risk factors (combination strategy) to be the most cost-effective in the Netherlands. Despite the activities undertaken to improve implementation, adherence to EOGBS preventive strategies remains poor when treatment is required (so-called under treatment).

This VIMP study aimed to provide more insight into the factors related to the diversity in (non-) adherence to preventive EOGBS strategies, an overview of existing knowledge on current and possible future preventive strategies as well as to identify knowledge gaps.

An online focus group was undertaken in three regions in the Netherlands inviting all care professionals involved. This showed that the reasons for the diversity in (poor) adherence per strategy and target population can be explained by lack of knowledge, and care professionals who find it difficult to translate a sense of urgency into action and to shed old routines & habits when policy doesn't necessarily improve outcomes in their view.

Others studies have shown that prematurity and complex protocols contribute to poor adherence. A substantial part of the non-treated cases appear to be unavoidable even with perfect protocol adherence even with perfect protocol adherence due to the (short of) length of labour. Although generally, existing international guidelines are of good quality, the different management options are a reflection of the low level of evidence on which they are based. A new Dutch National paediatric guideline on the prevention of neonatal infections including EOGBS is expected to be published in 2017.

Future developments concentrate on the availability of the rapid PCR test, concentrating preventive strategies on the more virulent GBS strains and a vaccine for GBS. Available studies show promising results for the rapid PCR test which can be made available at a 24 hours available point-of-care resolving some of the adherence issues. Although the rapid PCR has already been shown to be cost-effective in a hypothetical model, a cost-effectiveness study of the PCR in daily practice still needs to be undertaken in the Netherlands. The general consensus amongst researchers and experts is that the introduction of the rapid PCR test for GBS is timely and should be considered.

If knowledge on the specifics of guidance (and the proposed strategy) remains low and uniformity in the utilization of protocols is not achieved, prevention of EOGBS will not increase. Irrespective of the chosen strategy, rigorous renewed effort should be undertaken with regard to implementation and adequate adherence to the proposed strategy. The implementation needs to be concentrated on improving knowledge of an unambiguous protocol that facilitates the users and ensures a multidisciplinary approach.

Samenvatting

Early-onset Groep B- hemolytische streptokokken infectie (EOGBS) is een belangrijke oorzaak van neonatale morbiditeit en mortaliteit tijdens de eerste levensweek. Maternale kolonisatie tijdens de zwangerschap wordt in Nederland geschat op ongeveer 20%. Ongeveer de helft van de kinderen die geboren worden bij deze moeders, wordt ook gekoloniseerd, slechts 1% van deze kinderen zullen ziek worden ten gevolgen van EOGBS. Primaire preventie van EOGBS is mogelijk door middel van toediening van antibiotica tijdens de baring (IAP). Er zijn verschillende strategieën beschikbaar om vrouwen die IAP nodig hebben te identificeren. In Nederland blijkt de risicostrategie (IAP indien een van de vijf risicofactoren aanwezig is) en combinatiestrategie (IAP wanneer een van de vijf risicofactoren aanwezig is in combinatie met een positieve screeningstest), het meest kosteneffectief. Ondanks de ondernomen activiteiten om implementatie van GBS preventie strategieën te bevorderen, blijkt de adherentie aan dit beleid matig vooral daar waar behandeling geïndiceerd is (zogenaamde onderhandeling). Dit VIMP onderzoek heeft als doel meer inzicht te verwerven naar de diversiteit van factoren die van invloed zijn op deze (non-) adherentie; een overzicht van bestaande kennis en toekomstige mogelijkheden rondom de preventiestrategieën te geven en kennislacunes te identificeren.
Het online focusgroep onderzoek dat in drie verschillende regio's werd gehouden, liet zien dat matige adherentie verklaard kan worden door een gebrek aan kennis bij zorgverleners die het bovendien lastig vinden om een gevoel van urgentie om te zetten in actie en om oude gewoontes los te laten omdat beleid in hun ogen niet altijd tot betere uitkomsten leidt.

Andere studies hebben laten zien dat prematuriteit en ingewikkelde protocollen bijdragen aan matige adherentie aan preventief EOGBS beleid. Echter een substantieel deel van de niet-behandelde casus lijken door (korte) duur van de baring niet te kunnen worden voorkomen, ook niet met het perfecte protocol.
Alhoewel bestaande internationale richtlijnen over het algemeen van goede kwaliteit blijken te zijn, geeft de verscheidenheid aan beleidsopties blijk van het gebrek aan voldoende bewijskracht waarop de richtlijnen zijn gebaseerd. In de loop van 2017 wordt een nieuwe richtlijn infectiepreventie, inclusief EOGBS, van de Nederlandse Vereniging van Kinderartsen (NVK) verwacht waarin de preventie van EOGBS uitgebreid wordt besproken.

Toekomstige ontwikkelingen rondom de preventie van EOGBS concentreren zich vooral op de beschikbaarheid van de PCR sneltest, beleid gericht op de meer virulente GBS stammen en het ontwikkelen van een GBS vaccin. Beschikbare studies laten gunstige resultaten zien voor de PCR sneltest die met succes 24 uur / dag op een geschikte locatie beschikbaar kan worden gemaakt waarmee een aantal van de non-adherentie factoren kunnen worden opgelost. Alhoewel de PCR sneltest kosteneffectief is gebleken in een studie met een hypothetisch cohort , dient de kosten effectiviteit in de dagelijkse praktijk nog verder worden onderzocht voordat deze test op grote schaal kan worden geïmplementeerd. De algemene consensus onder experts en onderzoekers is, dat de introductie van een dergelijke test overwogen dient te worden.

Indien specifieke kennis van de betreffende richtlijnen en protocollen laag blijft en uniformiteit in het gebruik van protocollen niet wordt bereikt, verbeterd de preventie van EOGBS niet. Het is daarom van belang dat, onafhankelijk van de gekozen strategie, ruime en hernieuwde aandacht uitgaat naar de implementatie en adherentie van het gekozen beleid. Implementatie moet zich vooral richten op het verbeteren van de kennis van een ondubbelzinnig en helder protocol met een multidisciplinaire aanpak.

Contents

1 Introduction

Although the incidence is very low, 0.019- 0.12 %, early onset Group B- haemolytic streptococcus infection (EOGBS) is an important cause of neonatal morbidity and mortality within the first week of life. The case fatality rate of children with EOGBS is around 8% (1-3). According to Bekker et.al. the incidence of invasive group B streptococcus infection in children increased from 0.20 per 1000 livebirths in 1987, to 0.32 per 1000 livebirths in 2011 ($p<0.0001$).

Maternal colonization rates during pregnancy vary between 6.5% and 36% and are estimated to be around 20% in the Netherlands (2,4). However GBS colonization is not always pathogenic: 50% of the children of colonized mothers will become colonized during labour and of those, 1% will develop EOGBS (2). The odds-ratio's for EOGBS when the mother is GBS positive, vary between 4,36 to 37,0 (5).

Primary prevention of EOGBS is possible by administering IAP, however the Cochrane review reported considerable bias in the studies that showed a reduction in EOGBS with intra partum antibiotic prophylaxis (IAP) (6). Internationally different prevention strategies are used based on identifying pregnant women at risk either through screening for GBS colonization and/or through detection of risk factors for EOGBS in pregnancy or during labour (table 1), but available evidence on which policy is based remains poor (3,7).

Table 1: Overview of the core elements of four preventive EOGBS strategies

Core elements	Risk based strategy	Combination strategy	Dutch guideline	Screening strategy #
Identification of EOGBS risk factors*	Yes	Yes	Yes	No
Maternal GBS screening during pregnancy at 35-37 weeks gestation	No	yes	No	Yes
Cultures taken during labour	No	No	Yes during labour in women with risk factor 4 or 5*	No
Intra partum antibiotic prophylaxis (IAP)	All women with ≥ one risk factor	All women with GBS colonisation AND ≥ one risk factor	All women with risk factor 1,2 or 3. All women with risk factor 4 or 5* *AND* GBS colonization	All women with GBS colonisation
Observation of the baby when mother received IAP	Yes	Yes	Yes	Yes
Antibiotic treatment of baby	All baby's with signs of neonatal infection	All baby's with signs of neonatal infection	All baby's with signs of neonatal infection	All baby's with signs of neonatal infection

*1. Previous child with EOGBS, 2. GBS bacteriuria in current pregnancy, 3. Intra partum fever (≥38°C), 4. Preterm birth (<37 weeks), 5. Rupture of membranes >18 hours. # not tested in Responz-study.

Furthermore, preventive strategies are complicated by the fact that over 40% of neonates who develop EOGBS are born to mothers without a risk factor (2,8,9) (risk-based strategy, combination strategy and Dutch guideline), the sensitivity of the methods to detect GBS in pregnant women is low and accounts for a consistent proportion of EOGBS cases (8,10,11) (risk-based strategy, screening strategy and the Dutch guideline), large numbers of women receiving antibiotics (screening strategy) with possible negative side-effects such as antibiotic resistance (8) (based on the difference between application of antibiotics to all GBS colonized women or to a selection of GBS colonized women with a risk factor) and premature cases are missed when GBS screening starts from 35 weeks of gestation onward (screening strategy and combination strategy).

In 2009, a cost effectiveness study showed a strategy with IAP treatment based on five risk factors (risk based strategy) or based on a positive screening test in combination with one or more risk factors (combination strategy) to be the most cost-effective in the Netherlands. IAP treatment for all pregnant women with a positive GBS culture in pregnancy (screening strategy) and management according to the current Dutch guideline (IAP after establishing a positive culture in case of prelabour rupture of membranes or preterm birth and immediate IAP in case of intrapartum fever, previous child with EOGBS or GBS bacteriuria), were not shown to be cost effective in this study (12). The cost effectiveness in this study was based on the assumption of 100% adherence to each strategy.

Adherence to EOGBS prevention strategies was examined during the period of 2014-2015 in three regions in the Netherlands (Responz-study) (13). Using a pre- post-test design, the overall adherence in the three regions combined increased from 88% to 91% during the study. Under treatment did not decrease (8%) and less overtreatment was seen (from 5% to 2%) (14).
The risk based strategy showed the highest *overall adherence* (92.7%) compared to the adapted Dutch guideline (86.8%) and the combination strategy (81.3%). *Under treatment* was seen more often with the use of the adapted Dutch guideline when compared to the other strategies. O*ver treatment* was seen more often with the use of the combination strategy when compared to the risk based strategy and the adapted Dutch guideline (see table 2).

Results of the subsequent cost effect analysis based on *true* adherence, show that most EOGBS cases are prevented in the combination strategy. However, this strategy is expensive as screening costs are high. The results of this study show that antibiotic prophylaxis is given mainly to GBS carriers who are in labour at term and is not given to GBS carriers in preterm labour. It might be possible that overtreatment is directly linked to the observation of children from GBS positive mothers without a risk factor. On the other hand, care providers had a tendency to register symptoms of neonatal infection better during the trial period when compared to the pre-test registration indicating more awareness / accurate observation in the study situation, although this difference was not found in the other two strategy regions.

Table 2: Core results Responz study (14)

Core study elements	Risk based strategy	Combination strategy	Dutch guideline
Adherence (overall pre-test adherence: 87.6%)	**92.7%**	81.3%	86.8%
Under treatment	7.3%	5.7%	**9.9%***
Over treatment	0%	**13.0%***	3.2%
Cases prevented	80	**130**	67
QALY's gained	92	**113**	93
Costs per QALY gained	8.635	**121.485**	-134.312
Costs per QALY gained if birth costs are equal in all regions	43.902	**103.097**	43.902

*9.9% (p=0.04 when compared with combination strategy) 13.0% (p<0.001 when compared with other regions)

The conclusion of the Responz study is that despite the activities undertaken to improve implementation such as training of health care professionals, management flow-charts and reminder-cards for maternity-care assistants, the adherence to EOGBS preventive strategies is still moderate to poor when treatment is required (so-called under treatment). It remains unclear which preventive strategy is the most preferable strategy to implement nationwide. More insight in the reasons for non-adherence in all strategies is needed.

Given the moderate to poor adherence in the study of all prevention strategies for *women needing treatment*, it seems warranted that before a new guideline is introduced in the Netherlands insight into the reasons for the diversity in (poor) adherence per strategy and target population is gained and to provide an overview of the existing knowledge on current and possible future preventive strategies.

The aim of the VIMP study is to provide an overview of the factors related to the diversity in (non-) adherence to preventive EOGBS strategies, a literature overview of the existing

knowledge on current and possible future preventive strategies as well as to identify knowledge gaps. This knowledge and the extra information on top of the results of the Responz study generated by the VIMP-project, were discussed at an invitational conference: the conclusions of which can be used to formulate advice for the implementation of the most appropriate EOGBS preventive strategy in the Netherlands.

2 Online Focus Group Study

2.1 Aim

(In depth) identification of barriers and facilitating factors related to the implementation of EOGBS preventive strategies.

2.2 Method & Analysis

2.2.1 Design

To identify possible factors related to the diversity in management, adherence and implementation , a sample of inadequately treated / non-adherence GBS cases from the implementation study , will be analysed together with the care providers involved per region (primary care midwives, hospital based midwives, obstetricians, paediatricians).

A qualitative design was chosen to investigate and to identify possible factors related to the diversity in management and in particular the non-adherence to the three policies used in the (study)protocol for the prevention of EOGBS (13). This allowed for a more in-depth exploration of the extent to which this policy is implemented and how or if the core elements of EOGBS prevention policy are carried out. The qualitative design was combined with an exploration of the conceptual use of the assigned EOGBS policy by applying the MIDI implementation instrument as developed by Fleuren et al (15).

Willingness to participate was less than expected due to time constraints on behalf of the health professionals. Moreover the relative short time available within the project also limited the possibility of carrying out an audit of cases of non-adherence as proposed. Instead online focus group discussions, one per study region, were planned which encourage and enable health care professionals with busy and irregular work schedules to attend the discussion at a convenient time. This is particularly useful for overcoming the barrier of distance. While discussion is constrained, the written format can help with reporting on the discussion. Although less methodical compared to an audit meeting, they still allow for the exploration of research findings and the range of opinions/views on the topic of interest that cannot be explained statistically. However sufficient inclusion still remained difficult to achieve.

2.2.2 Participants

Participants were recruited from the three study regions used in the larger EOGBS Responz-study which investigated a cost-effective strategy for the implementation of EOGBS **VIMP-implementation project Responz-study** prevention (13). Primary care and hospital based midwives, gynaecologists and paediatricians were invited to participate on the basis of involvement with three true case histories from each region that were exemplary for non-adherence.

The online discussions were held asynchronously: Participants were able to access the discussion 24 hours per day during one full week (seven days) and were encouraged to interact with each other. New topics were introduced on a daily basis. The discussion was moderated by two researchers (DK & SJ).

Although identity of the participants was known to the moderators, participation was on the basis of anonymity to other participants. Preparation was not required although participants were encouraged to check for client details in their own files (on the basis of the assigned case number in the main study). Prior to the online discussion, participants received log-in instructions and anonymized case-histories by email. They were informed about anonymous participation, the possibility of opting out at any moment and data processing.

To stimulate active involvement, a surprise gift was introduced for the participant with the largest contribution to the discussion.
One focus group failed due to lack of participants despite several reminders. The two health professionals that were interested were individually interviewed by telephone.
After the focus group discussions were completed, regions were visited by the two moderators (SJ & DK) to enable triangulation. Regular regional meetings and venues organized by the local Obstetric Collaboration Group (OCG) were used for these discussions and the dissemination of results.

2.2.3 Topic list

The key activities in all preventive strategies (see table 1 on page 7 of this report) guided the topic list and the content of the discussions. The topic list was constructed on the basis of the implementation instrument as designed by Fleuren et al. which was also used during the initial study by Kolkman et al (13,15). The instrument contains potentially relevant determinants that can be interpreted as barriers or facilitating factors associated with the following four elements: the preventive strategy (the innovation), the users, the organizational context and the socio-political context.
See appendix 1. for complete topic list.
Three individual case histories of non-adherence per region were chosen from the data of the original study. This was done by selecting every fifth case of non-adherence in the data-base (n=232). Final selection was made on the basis of variety in key-elements (table 3)

Table 3: Selected case histories

Region 1 **Risk-based strategy**	**Region 2** **Combination strategy**	**Region 3** **Dutch guideline**
Primipara, planned home birth At 38+4 weeks gestation SROM followed by contractions. Baby born at home (in good condition) after 27 hours of SROM. General observation of baby at home. *Non adherence: no IAP despite risk factor, no intensified observation of baby*	Multipara cystitis at 34 weeks gestation, cultured but results unavailable. Regular culture set handed out to client according to GBS protocol but probably never carried out. Induction of labour at 39 weeks gestation because of unstable transverse presentation, resulting in CS. Baby 48 hours observation neonatal care. *Non adherence: no cultures taken and no IAP in case of unknown cultures*	Multipara, planned home birth. At 33 weeks gestation MRSA cultures: unknown reason. SROM at 39 weeks gestation followed by contractions. Baby born at home after > 18 hours SROM. *Non adherence: No cultures taken during labour despite risk factor, no further transfer.*
Primipara, history of cystitis. Start contractions at 35+6 weeks gestation, transfer to secondary care, followed by SROM. Baby born > 20 hours SROM. Observation baby neonatal care.	Multipara, At 35 weeks gestation suspected SROM but not confirmed. At 36 weeks gestation transfer of care because of reduced foetal movements. Standard GBS culture set handed out according to protocol.	Primipara. At 37+6 weeks gestation SROM at 39+1 weeks gestation, consultation secondary care because of dubious meconium stained liquor> not confirmed + return to primary care. In evening similar observations: transfer

Region 1 Risk-based strategy	Region 2 Combination strategy	Region 3 Dutch guideline
Non adherence: No IAP despite risk factor	Spontaneous start of labour at 38 weeks gestation, GBS results unknown, new cultures taken. Elevated temperature of 38 C. Baby born by CS *Non adherence: No IAP in case of unknown cultures*	secondary care followed by spontaneous labour. Augmentation and ventouse extraction. SROM > 18 hours. *Non adherence: Culture results unclear.* NB. In retrospect it appeared that cultures were taken: caregivers had adhered to strategy.
Multipara, history of cystitis, ? history of GBS with previous child. Urine culture initiated by GP at 32 weeks gestation is positive but result not within definition of GBS+. Management in consultation with obstetrician remains in primary care unless > 18 hours SROM. At 39+1 SROM, no contractions, transfer to secondary care after 12 hours to prevent transfer in the middle of the night. Baby born by CS after > 18 hours of SROM. *Non adherence: no IAP despite risk factor, no observation baby.*	Multipara, history of cystitis. Standard culture set handed out at 34 weeks gestation. SROM at 35+6 weeks gestation, followed by spontaneous labour. Culture results unknown (not recorded in patient notes), Discharge letter mentions positive GBS result. *Non adherence: No IAP despite either unknown culture or unregistered GBS positive culture*	Primipara. At 37 weeks suspected cystitis not confirmed. Spontaneous labour at 42 weeks gestation, SROM. Transfer of care because of pain relief request. Elevated temp of 38.1 C. Tachy-cardic CTG. Start Anti-Biotics. Spontaneous Vaginal Birth. Admitted to neonatal ward with suspected infection. *Non adherence: No cultures taken during labour despite risk factor.*

GP=general practitioner, SROM=spontaneous rupture of membranes, CS=cesarean section, IAP=intrapartum anti-biotic prevention, MRSA=Methicillin Resistant Staphylococcus Aureus, CTG=cardiotocography.

2.2.4 Analysis

The online discussions were fully downloaded. The telephone interviews were audio-recorded and fully transcribed ad verbatim.

Analysis was carried out by three researchers (MF, MR & SJ)). The online-focus groups were independently coded by two researchers (MF & SJ) and subsequently discussed. A difference of opinion was resolved by reaching consensus. Coding was carried out using the four elements and the determinants of the implementation instrument which guided the evolving themes. A frequency analysis was carried out to determine the most important determinants and subsequent themes. These results were discussed in a wider context with the researchers involved.

Results are categorized according to the elements of the implementation instrument. Themes, based on the identified determinants, are described and illustrated with corresponding quotes. Background of participants is indicated in brackets.

The primary study was approved by the National Central Committee on Research involving Human Subjects (CCMO NL 41673.058.12) and by the ethics committee of the Leiden

University Medical Centre (ref. no P12.184). Medical-ethical approval for this sub-study was therefore not deemed necessary.

2.3 Results

Two online focus group discussions were held with thirteen participants: seven primary care midwives, two hospital based midwives, two gynaecologists (one of whom failed to contribute to the online discussion but was briefly interviewed by telephone in a non-structured manner) and two paediatricians. We failed to reach sufficient inclusions for the third online focus group. The two health care professionals, primary care midwives, that were available were individually interviewed by telephone (SJ) during which the online topic guide was used as an interview guide.

Three regional meetings took place at three different non-academic regional hospitals and were well attended by primary care and hospital based midwives, gynaecologists, paediatricians and one obstetric nurse. All are members of the local OCGs

From the focus groups it emerged that most determinants of non-adherence were associated with the elements “the innovation” (n= 74) and “the user” (n= 81) and were negatively interpreted, i.e. policy was misunderstood, incomplete or unsupported by health care providers. Few determinants (n=9) were associated with the organization concerned with the prevention of EOGBS. No politically motivated determinants were identified. In total fewer determinants were identified in Region 3, which was the region with insufficient participants for the online focus group resulting in a minimal amount of data (table 4).

Table 4: Determinants related to identifying risk factors or screening for GBS colonization, mentioned by care providers (p=positive, n=negative)

Implementation element [ref Fleuren etal 2014]	Determinants	Region 1 Risk-based strategy P/N	Region 2 Combination strategy P/N	Region 3 Dutch guideline P/N *
The innovation	1.Procedural clarity (guideline)	3+ / 15-	1+ / 5-	*0*
	2. Correctness	8-	2+ / 1-	*4+/1-*
	3. Completeness	11-	1-	*0*
	4. Complexity	1-	3-	*0*
	5. Compatibility with current guideline (guideline)	5-	1+ / 6-	*2-*
	6. Visibility of results	1-	0	*0*
	7. Relevance for client / patient	1+ / 2-	0	*0*
	Total (n= 73)	**4+ / 43-**	**3+ / 17-**	**4+ / 3-**
The User	8.Personal benefits / drawbacks	0	0	*0*
	9. Outcome expectations	2+ /14-	1+ / 14-	*1+ /3-*
	10.Taskorientation	0	1-	*0*
	11.Client/patient satisfaction	2+ / 1-	2+ / 3-	*0*
	12.Client/ patient cooperation	3-	2-	*1-*
	13.Social support by other care provider (user)	2+ / 7-	2-	*2+ /3-*
	14. Descriptive norm	2-	1-	*1-*
	15. Subjective norm	0	0	*0*
	16. Self-efficacy (user)	2-	0	*0*
	17. Knowledge (user)	2-	0	*0*
	18.Information	2+ / 6-	1+ / 1-	*0*
	Total (n=81)	**8+ / 34-**	**4+ / 24-**	**3+ / 8-**
The organisational context	19. Formal ratification by management	0	0	0
	20. Staff replacement	0	0	0
	21.Staff capacity	0	0	0
	22. Financial capacity / resources	0	1-	0
	23. Time	3-	1-	0
	24. Material resources	2-	2-	0
	25.Coordinator	0	0	0
	26. Organizational turbulence	0	0	0
	27.Available innovation information	0	0	0
	28. Available user feedback	0	0	0
	Total (n=9)	**5-**	**4-**	**0**
The socio-political context	29. Rules & regulations	0	0	0

Three main themes emerged from the discussions clustering the identified determinants: Old habits die hard, Failing to grasp the protocol and weighing the balance.

2.3.1 *Old Habits die hard*

Participants, especially primary care midwives found it hard to adhere to new elements in the protocol (determinant 5). Participants mentioned (quite firmly at times) that they were unconvinced by the evidence (determinant 9). Particular disagreement was expressed with the eighteen hour cut-off point for transfer to secondary care after pre-labour rupture of

membranes (PROM) to enable culture taking a.o. as opposed to the accustomed cut-off time of 24 hours (16,17).

> *Yes but that is not a , if that never has been a reason than we are not already going to culture after 18 hours?! (…) but I already said before [the start of the main study], that I wouldn't do that I wasn't going to do anything extra. (Primary care midwife Region 3)*

> *Do you mean to tell me that our guidelines say that when someone has more than eighteen hours PROM, that they have to be cultured ?! [disbelieve and clearly exasperated] (Primary care midwife Region 3)*

> *… only it was sometimes awkward with eighteen hours PROM and being in labour, normally your management would be 24 hours of PROM and you think, yes well, do I have to transfer, I sometimes thought that was an issue because in your mind you still think 24 hours…(primary care midwife Region 3)*

> *… not wanting to disturb the natural / physiological birthing process and when the birth of the baby is expected within a short amount of time, around eighteen or 24 hours of PROM, you don't transfer.(Primary care midwife Region 1)*

Disagreement and non-adherence was especially apparent in cases of normal labour with PROM and in which a normal vaginal birth was expected. In these circumstances more than eighteen hours of PROM was not seen as a risk factor or rather the iatrogenic risks of a transfer were thought to be bigger than the EOGBS risk in this case. Clearly outcome expectations (determinant 9), were different compared to what is described in all three protocols: i.e. the risk of infection was thought to be low.
The same argument was put forward for the length and / or type of observation of the baby when this was indicated. Maternity care professionals were led by practicalities rather than strict adherence to the protocol. For example this meant that a convenient discharge time according to usual customs seemed to be the leading argument, as opposed to strict adherence to the protocol. The same argument was also used for the decision when to transfer in case of PROM.
Furthermore professionals actually disagreed with the practical origination of care within a protocol as shown by the following quote:

> *And then if you think about the fact that observation in the hospital only consists of checking respirations and temperature three times a day, then I understand that a maternity aid nurse, who can provide one-to-one care right from the start at birth and can continuously observe the child, is able to assess the child as well in which case the child can be admitted when sick.(Primary care midwife Region 1)*

2.3.2 Weighing the balance

Focus group participants and maternity care professionals present at the OCG meetings acknowledged the importance of adequate prevention policy / management. They showed considerable surprise about the extent of non-adherence shown in the results of the Responsz study as they all felt that they were vigilant towards GBS policy and actively used the protocol. Some participants even expressed doubts about the correctness of the study results, whereas others were willing to address the issue but mentioned the need for consistent national policy. Participants were all well aware of the seriousness of EOGBS, they weighed risk factors against their clinical judgement of the overall birth progress. This may explain why despite the sense of urgency based on the seriousness of EOGBS, does not seem to be translated into

action. This is underlined by the negative score of 28 on determinant 9 in table 3 (outcome expectation). And is also apparent from remarks made about the medicalization of childbirth: participants thought this a more serious issue and felt that applying the intervention would be counterproductive to a good birth outcome.

> *… but if they don't end up in hospital, you actually never see sick children. Only very seldom do you really have a sick child at home […] may be that is my experience after being a midwife for more than 38 years. [very adamant] (primary care midwife Region 3)*

> *… it has to do with ourselves: the routine was insufficient to be alert in order to take cultures and we doubted the proposed strategy: to culture all women can medicalize a healthy population. (Primary care midwife Region 2)*

Not just midwives were concerned with medicalization of child birth. One paediatrician wanted to explain that he questioned the policy of keeping an obviously healthy child admitted to the hospital and another was concerned about the impact over-treatment:

> *I can report that this neonate must have reacted very well on all fronts otherwise we would have never discharged a 36 week old baby of a primip. (Paediatrician Region1)*

> *BS can have serious signs and symptoms in the neonate. Only, all antibiotics disturb the microbiome of mother and child. More and more is known about the importance of the microbiome for the prevention of diseases such as diabetes, obesity etc. Because not enough is currently known, the balance can tip to more frequent treatment of mother and / or child but this may be wrong in hindsight. The disadvantage of cultures is over-treatment. (Paediatrician Region 2)*

Midwives weren't convinced that removing women from their comfortable home environment would result in better care if adequate treatment could not be achieved (determinant 9), further supporting the conviction that the protocol medicalizes childbirth and which again illustrates the careful weighing of several ongoing issues:

> *Transfer to secondary care, in which case a woman needs to be observed first, so that means first a 20 minute CTG, a vaginal examination followed by a consultation and discussion with the hospital midwife or obstetrician whether or not to start antibiotics. So delay and new faces at the bedside. (Primary care midwife Region 1)*

A transfer during labour only to be able to take cultures during birth, as prescribed by the protocol in region 3, was not thought to be beneficial since results would never be available on time.
Another paediatrician during the discussion at the regional meeting (Region 1) explained that medicalization was expressed by Numbers Needed to Treat (NNT): if the numbers are large he / she was more willing to deviate from the protocol especially if the clinical signs showed a healthy baby because, on the basis of experience, this would benefit the outcome for that baby and its family. The advice of the health professionals in this region was to add information to the protocol how many women need to be treated / babies observed to prevent one case. Another suggestion was to not only describe the advantages of the intervention in the protocol but also to add a description of the disadvantages. This was indirectly mentioned by one of the midwives:

> *When do you have health benefits? I find this difficult to judge. Do you want to treat a certain percentage as opposed to the percentage of sick children or something?(Primary care midwife Region 2)*

> *Apparently there are more pregnant women who are GBS carriers than we thought. I only wonder, when you culture everyone, do you actually gain health benefits or would it medicalize childbirth unnecessarily and at higher health care costs? My impression was that it caused a lot of unrest amongst pregnant women. My feeling was that I needed a lot of time to explain what exactly GBS is to women and reassure them. (Primary care midwife Region 2)*

When cases were complex (determinant 4); other priorities took over which resulted in EOGBS related interventions to be forgotten:

> *… in this case history other things played a role with a bigger priority at that moment, I think that is why the cultures were forgotten. (Primary care midwife Region 2)*

On the other hand cultures taking during pregnancy also caused a lot of unrest as the subject was discussed with women who would otherwise not be informed about GBS:

> *I think the information that was provided [via the leaflets that were part of the main study] was adequate, only it wasn't always apparent how many people actually read the information. It caused a lot of unrest and gave rise to many questions, but that may also be because it was new. If this becomes a regular investigation during pregnancy, the newness will go and pregnant women will be less worried. (Primary care midwife Region 2)*

For women in premature labour the screening protocol underlined another problem, one regarding the non-availability of results:

> *According to the lab it [the culture] needs at least two days. The essence of this case is that we didn't know the woman was GBS positive. Had we known, we would have given the mother antibiotics…(Paediatrician Region 2)*

This comment was made in relation to a premature birth, before results of the screening in pregnancy could be available. This was also underlined by the fact that actions / interventions to be taken in the hospital can take a long time before they are initiated.

2.3.3 Failing to grasp the protocol

Participants felt that the procedures described in the protocol were insufficiently clear (determinant 1). They either expressed to be unaware of the contents of the protocol or it was apparent from their statements that they were insufficiently aware of the protocol. It was also mentioned that guidance was insufficiently based on evidence (determinant 2 & 17). Some thought the protocol was incomplete (determinant 3).

> *[…] the protocol does not explicitly mention the relevance of uterine contractibility or contractions after eighteen hours of ruptured membranes for the decision to transfer. (primary care midwife Region 1)*

> *This case history shows that implementation of a complex protocol needs extensive training and clear flowcharts. The situations in which an unknown carrier status needed to be dealt with, caused a lot of confusion. (Obstetrician Region 1)*

> *[…] It [the protocol] doesn't mention if observation of the neonate should be carried out on the neonatal ward or on the postnatal ward. (Primary care midwife Region 1)*

> *This case history shows the necessity of a clear flowchart and adequate schooling when the protocol is complex. (primary care midwife Region 1)*

> *In order to implement the protocol, it has to be clear to me that this [policy]will result in fewer complications. I would also like to see a cost effectiveness analysis, both financially as well as all the (dis-) advantages of the strategy that is to be followed. (primary care midwife Region2)*

A lot of so-called loose ends in the protocol were mentioned by one participant who advised to address these, such as: *do we still need a urine culture with a positive rectovaginal culture?* (obstetrician) Or: *If someone was GBS positive during her previous pregnancy, is she now still to be treated as EOGBS positive? (midwife).*
One participant didn't realise he / she was actually correctly stating the contents of the protocol:

> *I don't find the GBS-status interesting without any risk factors (Paediatrician Region 2)*

Insufficient clarity and incompleteness of the protocol was most frequently mentioned by the participants who worked in the region with the Risk-based strategy (Region 1 compared to Region 2). The protocol in this region was the protocol that was most incompatible (determinant no.5) with the current guideline (18).

2.4 Discussion

From the focus groups it emerged that most determinants of non-adherence were associated with the elements "the innovation" and "the user" and were negatively interpreted. Old habits die hard; Weighing the balance and Failing to grasp the protocol were the themes that emerged from the discussions. They describe that caregivers found it hard to adhere to the elements in the protocol and especially midwives used their clinical knowledge to weigh the effect of the required intervention. More, despite the fact This may be the reason that participants despite their awareness of the seriousness of EOGBS, this is not always translated into action.
Despite the easy access to an online environment and several reminders both before and during the online discussions, it was difficult to motivate care providers to participate in the study. Although online focus group research is particularly useful in overcoming the barrier of distance and time, the written format also requires more effort from participants to really think and to be eloquent about what they want to add to the discussion. This constrains the discussion as it takes away spontaneity(18), possibly creating a barrier for participation. Moreover the larger initial Responz study was carried out two years before this qualitative study, making it hard for participants to recall events pertaining to a particular case history. Poor participation possibly also underlines the third theme of "Unfelt urgency": EOGBS is clearly seen as a serious condition but in the line of priorities, it does not appear to rate very high.

Caregivers in this study, especially primary care midwives, were very sensitive about the medicalization of childbirth also because there was little understanding for the need to transfer since culture results are not immediately available, partly because the test needs time which is not improved by the fact that the microbiology lab is only available during office hours (region 3).

Currently there is much debate about the introduction of the rapid GBS Polymerase Chain Reaction (PCR) test for intrapartum testing (19). Providing the test is 24/7 accessible, this would considerably reduce the time-to-result.

Non-adherence caused by the incomprehension of the eighteen hour cut-off point for transfer of care in case of PROM should be re-addressed in view of the recent publication by the midwives organization, stating 24 hours to be the most appropriate cut-off point (16). Moreover, it is incompatible with current policy (determinant 5) which was something mostly mentioned in the region with the risk based strategy. However non-adherence also appears to be caused by practical factors such as not wanting to transfer in the middle of the night regardless of proposed cut-off point. It is difficult to determine when non-adherence is a result of “Old habits die hard” or when it it is the result of “Weighing the balance.” Non-adherence could be questioned when the balance is carefully weighed by a health professional, since this is can also be the result of valid clinical reasoning which is part of Evidence Based Practice. Important in this case is to document such decisions.

Despite extensive schooling at the start of the Responz study, caregivers appeared to be surprisingly ill-informed about the contents of the (study) protocol in their region. They mentioned the need for further training and education. The answer to the question why information was inadequately absorbed can possible be found when looking at the different stages of the implementation process as described by Grol and Wensink (20): Before a strategy is implemented the stage of the implementation process needs to be examined and an implementation strategy should be chosen accordingly. Knowledge contained in guidelines is only of limited value. Therefore when (new) GBS policy is introduced much more attention needs to go the implementation process and how this can be optimally supported.

Women or clients did not participate in this study but the participating health care professionals suggested that women may not always feel the urgency to test for GBS since culture results often did not come back to the care providers or the lab. Self-management with regard to GBS screening has been studied in other countries and found to be feasible (21-23), this possibility has not been examined explicitly in the Netherlands. The Responz study showed that women seem to be wary of over-treatment with anti-biotics and although the vast majority of women had no objection to taking a culture swab themselves, they felt a swab taken by the professional was preferable because of the expected better outcomes and physical difficulties if carried out by themselves (24), which is in concordance with the study results of Arya etal. (22). Whether or not this had anything to do with the failure to return swabs for culture during the Responz study, is unknown.

Although no consensus was apparent about which professional this should be, the need for clarity about who is responsible for culture results, was evident especially during the critical point of transfer. An issue which is currently much discussed at national level and which is related to integration of care, is the implementation of case managers (25) and the use of electronic case notes both of which would support the availability of test results.

Based on the results of this study, a future national policy guideline for the prevention of EOGBS, should take the points as described in table 5 into consideration.

Table 5: Suggested protocol improvements

Suggested improvements to protocol
1. Add NNT
2. Clearly describe advantages but also disadvantages of interventions
3. Distinguish between SROM with and without contractions
4. Distinguish parity with SROM
5. Re-address the cut-off point for the length of ruptured membranes > 37 weeks gestation
6. Clear definition of what constitutes a positive GBS culture
7. Besides length of observation of baby also describe where this observation can take place and under which circumstances
8. Clearly state whether or not urine cultures are needed on-top of a rectovaginal culture
9. Clear description of responsibilities of all health care professionals involved, including the health care professional responsible for the results of a culture
10. Clearly state the consequences of a positive GBS in a previous pregnancy (especially if culture in current pregnancy is negative)
11. Investigate the effects and possibilities regarding self-management of cultures

2.5 Conclusion

The reasons for the diversity in (poor) adherence per strategy and target population can be explained by on one hand lack of knowledge, and on the other hand care professionals who weigh the balance of interventions versus the effect and to shed old routines & habits when policy doesn't necessarily improve outcomes in their view. According to the results of this focus group study, implementation efforts with regard to the prevention of EOGBS should be concentrated around the elements of the innovation (improve knowledge of the protocol) and the users (midwives, obstetricians and paediatricians).
Whether self-management of GBS cultures is feasible in the Netherlands will depend on the chosen strategy. Culturing when labour or birth is imminent is often thought to be superfluous. This may be overcome by the availability of the rapid PCR-test.

3 Overview of current knowledge, available technologies and gaps in knowledge

The aim of this chapter is to give an answer to the following questions:

1. What is known about the levels of adherence to different preventive strategies for EOGBS?
2. What is known about enhancing and (the solution of) inhibiting factors of implementation of different EOGBS strategies?
3. What are the potential positive and negative effects of the most applied preventive EOGBS strategies?
4. What is known about the current and future developments regarding screening and maternal and neonatal treatment?
5. What are the current knowledge gaps.

3.1 Levels of adherence & influencing factors

Questions one and two about the levels of adherence to a chosen strategy and the influencing factors of adherence, have been answered by the Responz study which showed that in the Netherlands, overall adherence to EOGBS preventive policy is good but that specific adherence in case of a positive GBS status can be much improved upon for all three strategies (see table 2, page 9) (13,24). Both the Responz study and the subsequent VIMP study showed that enhancing and inhibiting factors mostly pertain to the elements of the innovation (knowledge of the protocol) and the users (midwives, obstetricians and paediatricians) and less so for organizational aspects(13,24) (also see previous chapter). The socio-political context was not found to be an issue. Lack of clarity of protocols was seen as an inhibiting factor. Caregivers felt that the definitions of a previous child with EOGBS and a positive GBS status should be better described. They wanted more details about the place and circumstances required for adequate observation of the baby post-partum when necessary and the procedures around PROM (also see table 5, page 20). Other inhibiting factors are concerns over the over-use of antibiotics, limitations to choice in place of birth caused by a specific strategy, and the limitations of culture taking during birth.
Caregivers felt capable of discussing EOGBS prevention policy and results with clients and they also felt capable carrying out the necessary procedures: these were seen as enhancing factors.

The Responz study also showed that the main reasons for choosing or declining a strategy for pregnant women were: risk of over treatment, negative effects for the woman or the child, the ability of early treatment in case of GBS positive woman and costs(24).
Caregivers expressed that the combination strategy would be the most preferred strategy to be introduced. Both women and caregivers felt that the screening strategy should not be introduced for fear of over treatment. Concern about antibiotic resistance is also shared by the Dutch government who initiated a new campaign to combat antibiotic resistance last year(26).

Other studies have also looked at adherence in a variety of settings. Berardi et al showed that women in preterm labour are less likely to receive IAP when indicated and that most unnecessary antibiotics are given in cases of PROM (10). An Italian study, based on the guidelines of the Centre for Disease Control (CDC) in the United States (US), showed that fully administered IAP was significantly more likely in women who had no previous live birth,

who gave birth vaginally, and who had a positive result at antenatal GBS screening, showing a substantial gap between optimal and actual IAP. According to the authors, the complexity of the CDC guidelines may partially explain this shortcoming (27). A study from the US (based on the CDC advised screening strategy), showed that a substantial part of the non-treated cases were unavoidable even with perfect protocol adherence. The cases that were avoidable mostly pertained to a time delay in administration of IAP (28). IAP is considered successful when given at least four hours before the birth of the baby (29).

Verani et al also investigated adherence in the US and found mostly errors in specimen collection (30). Intrapartum prophylaxis errors (not receiving IAP 38.2% and incorrect IAP 37.2%) were more commonly observed among preterm women than those who gave birth > 37 weeks gestation (54.1% compared with 13.5%, P,.001). Further investigations into the background of non-adherence were not carried out in this study.

An Irish risk based study also observed substantial non-adherence (58%), and also showed that non-adherence was even greater when labour was preterm (68%) (31). The authors demonstrated that administration of IAP increased in the presence of additional risk factors. It must however be noted that the study was limited to only three risk factors: preterm labour <37 weeks' gestation, PROM >24 hours, and pyrexia during labour (>38°C) and did not further investigate the reasons for non-adherence. In the Netherlands this may be caused by the fact that when labour is premature a different protocol to the EOGBS protocol is applied (32)

3.2 Effects of the most applied preventive EOGBS strategies

The potential positive and negative effects of preventive EOGBS strategies are summarized in table 6. None of the available strategies is perfect and none will prevent all cases of EOGBS. This was underlined again by the Cochrane systematic review by Ohlson et al, who concluded "*that Intrapartum antibiotic prophylaxis appeared to reduce EOGBSD, but this result may well be due to bias as we found a high risk of bias for one or more key domains in the study methodology and execution. There is lack of evidence from well designed and conducted trials to recommend IAP to reduce neonatal EOGBSD. All cases of EOD cannot be prevented."(6).* Although the risk-based strategy is best adhered to in the Responz-study, almost half of cases are missed when this strategy is applied and since not all maternal colonization's are pathogenic, the screening strategy is not ideal either.

Table 6: Positive & negative aspects of preventive strategies

Strategies	Numbers needed to treat per GBS case prevented[12]	Positive	Negative	Remarks
Risk based strategy	101	Best overall adherence in Responz study.	Cases are missed as 46% of neonates with EOGBS are born to mothers without risk factors.(2)	For women with previous GBS: time interval between the pregnancies and intensity of colonisation in previous pregnancy are predictive of recurrent GBS colonisation.
Combination strategy	62	Most preferred by caregivers and women, and most cases prevented. Best adherence in women with EOGBS risk factors.	Worst overall adherence. Highest costs / QUALY gained. Substantial impact on the provision of antenatal care.	Self-sampling is possible but most women prefer a health care provider to take the sample for culturing.
Dutch Guideline	98		Least cases prevented. Culture taking during labour only effective in case of threatened premature birth.	Most Barriers related to the user and the guideline / protocol itself (poorly described definitions & recommendations).
Screening strategy	142	All pregnant women are tested for GBS colonisation.	Overuse of antibiotics. Increased infections with antibiotic resistant organisms. Medicalisation of childbirth & neonatal period. Substantial impact on the provision of antenatal care. Risk of complacency in relation to women who screen negative.	Antenatal carrier status is a poor predictor of neonatal GBS disease since GBS colonisation is not always pathogenic. Colonisation can be transient. Insufficient evidence to decide whether screening for GBS carriage does more good than harm and that the benefits are cost-effective.

3.3 Current developments

The current NVOG Guideline dates from 2008 and has not yet seen an update (29). Since the publication of this guideline, professional organizations in England, the United States, Canada, New Zealand and Australia have published guidelines or statements regarding the prevention of EOGBS [see appendix 5]. Homer etal demonstrated a high overall quality of standards based on the AGREE II tool in the CDC, RCOG, Canadian and New Zealand guidelines (33). However all guidelines scored poorly on 'applicability': including barriers and facilitators to the application of the guideline, costs and auditing of implementation. The authors conclude by underlining the importance of these factors since they are fundamental in the adherence to the guidelines recommendations. Moreover, the different management options are a reflection of the low level of evidence on which they are based.

Recently the Dutch College of Paediatricians published a concept guideline for the prevention of early neonatal infections including EOGBS (5). The new guideline is an adaptation of the NICE guideline neonatal infection published in 2012 (7) but is considerably less transparent about the evidence levels (which are low) on which recommendations and guidance are based.

The NVK guideline advices to consider determination of GBS status between 35-37 weeks pregnancy when: GBS colonization was present in a previous pregnancy, a previous child was treated for early onset neonatal septicaemia or meningitis caused by unknown organism and respiratory or circulatory support was necessary. IAP should be given when GBS colonisation is confirmed (positive urine and / or recto-vaginal culture) in current pregnancy, if the woman has a previous child with GBS disease and IAP is to be considered when PROM occurs <37 weeks of pregnancy and GBS status is unknown. Despite remaining questions about cost-effectiveness and appropriate PCR-strategy, the guideline recommends the use of the PCR test for GBS, if available, when risk factors are present. A specific change in policy has been made in the new guideline to also discuss the possibility of IAP with the woman concerned when the a current culture is GBS positive but no other risk factors exist. This does give more autonomy to the pregnant woman herself, however concerns exist that this will increase (unnecessary) antibiotic use during labour (personal communication (34)).
In the meantime, at the beginning of 2017 NICE announced that an update of their guideline would be undertaken. NICE is updating the recommendations for risk factors for infection and clinical indicators of possible infection and the use of intrapartum antibiotics. They will also be adding a new area on maternal group B streptococcus status to guide the decision on timing of delivery in women with preterm prelabour rupture of membranes and extending the scope to cover antibiotic treatment for late-onset neonatal infection.
This means that the red-flag system on which the guideline is based, will also be updated.
Furthermore because of the low levels of evidence, guidelines have interpreted the evidence differently, which is an additional reason for NICE to update their guideline: The experts of the NICE guideline and the Green-top guideline of the Royal College of Obstetricians (RCOG) (3), agreed there is a discrepancy and that local practice is split. They noted that “there is not good evidence in this area and it has been interpreted differently by the Royal College and NICE” (35).

3.4 Future developments

3.4.1 GBS vaccination

All currently available prevention strategies are aimed only at the group of early onset GBS infections, not at the group of late onset infections. As the literature and the Responz study have shown, there are a number of challenges in the application of these strategies.
Antenatal vaccination (or vaccination before pregnancy) against GBS would be an interesting alternative to the presented strategies and could prevent neonatal GBS infection via vertical transfer of IgG antibodies.
However vaccine development has been challenging. A multivalent capsular antigen based vaccine is at present being tested in clinical trials: phase II development, awaiting phase III trial designs (36). On top of this a randomised trial is required to assess neonatal outcomes(37).
Three major pharmaceutical companies are currently developing a vaccine for immunization during pregnancy to prevent both early and late onset GBS disease and results seem promising (36). In the Netherlands microbiologists in the Academic Medical Centre (AMC) are working on studies to complement the GBS vaccine development research (1). This group is

also studying the more virulent strains at which new treatment and management is aimed (see also report of GBS Invitational Conference on page 34). Timing of when to vaccinate exactly and who would be the optimal candidates, still needs further studies.

Moreover, knowledge on the acceptance and women's attitudes towards antenatal GBS vaccination is limited. In 2016 McQuaid et.al. in England explored attitudes of fourteen pregnant women and eight women with GBS experience as well as 28 healthcare professionals. Although women were open and accepting to the idea of antenatal vaccination, they were also very cautious, leaning heavily on the existing knowledge that unnecessary medication should be avoided during pregnancy (38). Similar findings were found by researchers in the US (39).

3.4.2 *Rapid PCR-based GBS test*

One of the barriers for the implementation of and adherence to GBS strategies is that cultures during pregnancy have limited predictive value and cultures taken during labour (as is the case in premature births and PROM), often have little use since it is time consuming to wait for the results.
Scientists have been developing an intrapartum polymerase chain reaction (PCR) test for the detection of GBS which would greatly reduce the time-to-result from a median 70 to 1.5 hours (40). Results seem promising (see appendix 6). The rapid PCR test appears to have a similar sensitivity and specificity as the standard culturing methods.
The new NVK guideline hypothesizes a possible reduction in IAP use since the test could be used for women during premature labour (5). The phase II study by Hakansson, showed a possible decrease of the use of intrapartum antibiotic prophylaxis in a setting with a risk-based intrapartum antibiotic prophylaxis strategy (41). However this is not the current strategy in use in the Netherlands.
Most studies indicate however that the test needs skilled and adequate training of personnel and the institution of proper quality control (40-42). Authors also suggest that the more experienced a person is with the test the less indeterminate results (41). For obvious reasons the point-of-care (POC) should be available 24 hours / day.
If the test would be offered to *all* women in labour, 20% would have an indication for IAP. How many women in the Netherlands would have an indication for IAP when the test is carried out *on the basis of risk factor* during labour, is unknown. The effect on neonatal health is also not known.
The impression is that the implementation of a rapid PCR test might be cost-effective. However this has not yet been investigated, certainly not in the Netherlands.
Whether or not the PCR test would affect the adherence to the strategy will also have to be looked at in the future.

3.5 Current knowledge gaps

As several other documents have highlighted, the prevention of EOGBS is hampered by the lack of evidence [refs NICE, RCOG, Cochrane]. In the United Kingdom (UK) this has resulted in differences in management in the guidelines of two well established and highly regarded institutions (3,7).
According to the Cochrane review there is lack of evidence from well-designed and conducted trials which means that IAP during labour for women at risk on this basis cannot be supported. The Cochrane also points out that the opportunity to do so has probably been lost as practice guidelines have already been widely introduced (6).

The Lancet recently drew attention to the incidence of still birth, identifying that infections contributed an estimated 5-22% to still birth rates (43). Specific infections are not mentioned and little is still known about the effect of GBS on still birth rates in the Netherlands.
As described earlier, a rapid PCR test during labour appears to be a more accurate way of testing colonization, but evidence from studies assessing the validity and cost-effectiveness of this method is still lacking nor do we know anything about the short or long term effects such as the use of antibiotics. The use of antibiotics increasingly has the attention of the Dutch government because of fear of antibiotic resistance (26). If this method is fully in the future, adherence to the strategy needs to be investigated since no knowledge is yet available on this particular subject.
The effects of a positive maternal GBS status on the baby have more often been studied compared to the effect on the mother itself. Recently a UK study showed that severe maternal GBS sepsis is rare (incidence of confirmed severe maternal GBS sepsis 1:100 000 maternities) (44). Severe maternal GBS sepsis was associated with additional maternal morbidity, and was also associated with increased odds of infant sepsis and longer hospital stays. Similar studies in the Netherlands have not been found.

Currently if cultures are deemed necessary, they are generally carried out by health care staff. In the Responz study it was found that a swab taken by the professional was the primary choice of most women because of the expected better outcomes and physical difficulties if performed by themselves (24).
Self-management with regard to GBS screening has been studied in other countries and found to be feasible (21,23,45,46), although it is mentioned by participants of the VIMP study, this possibility has not been examined explicitly in the Netherlands.
Vaccination for the prevention of EOGBS does not seem to be imminent. Moreover before this is ever implemented, timing of when to vaccinate, who are the optimal candidates, the long term effects on both mother and baby and cost-effectiveness, still needs further studies, as well as Dutch women's views & attitudes on antenatal GBS vaccination.

4 GBS invitational conference

4.1 Aim

To create insight, awareness and possibly consensus regarding future EOGBS policy in the Netherlands and to generate discussion about the improvement of implementation of national policy of EOGBS prevention and the identification of knowledge gaps

4.2 Method

Invitations were sent to all professionals possibly involved with EOGBS research and / or policy. All participants in the three regions of the Responz-study were also invited, including maternity care organizations. Considerable effort was made to invite client representation but only the GBS-patient organization was able to attend.

Gynaecologists x5	Microbiologists x3	Health inspectorate x1
Paediatricians x5	Nurses x1	Policymakers x2
Midwives x 6 3 non-practicing, 2 clinical midwives, 1 primary care	Clients / patient organization X1	Researchers x2

The afternoon was held at a central location and was chaired by a gynaecologist / EOGBS researcher (Maurice Wouters).
The afternoon was centred around three presentations and aimed to generate discussion about national policy, implementation of EOGBS prevention and the identification of knowledge gaps. Discussion was encouraged by the use of three discussion points formulated by each of the three speakers (see appendix 4 for program).

4.3 Presentations and comments:

4.3.1 The new paediatric guideline (concept)

R. Kornelisse, paediatrician

An overview of the current situation of the prevalence of EOGBS in the Netherlands was presented as well as the **(concept) of the new paediatric guideline** which contains a specific chapter on EOGBS. The NVK (Dutch Society of Paediatricians) has applied for a grant to design a practice / consultation document to support clinicians in daily practice.

It is not the intention of the guideline to offer universal screening.
During the discussion participants mentioned that incidental findings are deemed important in the guideline but that despite this screening is not advised. The apparently contradictive message may cause confusion by users of the guideline. This is important given the potential effect of confusion on non-adherence as seen in the results of this VIMP. Furthermore, considering concerns over increasing anti-biotic resistance, a restrictive policy would be preferable.
Participants warned against unclarity and confusing recommendations in the guideline. To support correct implementation, clear and undisputable recommendations are to be formulated.

The authors of the guideline responded that awareness of the dangers of overuse of antibiotic and the possibility of creating resistance as well as the influence of antibiotics on the microbiome are important but also pointed out the seriousness of a sick child. This is a delicate balance to be maintained.
The question was raised how to involve pregnant women and / or parents in this discussion and what if antibiotics are refused?
Although some of the care professionals still seem to find this a difficult subject, the patient organization is pleased with the addition of shared decision making to the guideline. Counselling nowadays is an integral part of care and all professionals should be able to deal with difficult issues.
To doubt decision ability of clients / parents is belittling. Informing clients will also increase awareness of signs & symptoms which in turn should increase timely detection of sick children.
The question if the concept guideline was still subject to change was answered negatively, since the guideline is currently already in the authorization phase. Despite this the invited audience advised to take note of the discussion of today.

4.3.2 *Results of the Responz-study*

D. Kolkman, midwife and PhD student (See also introduction chapter, page 7).

The question was raised whether the characteristics of the third study group (NVOG guideline) were not marked by general non-adherence to guidelines or patterns in mal-adherence to strategies. This was not something the study could confirm.
The audience advised to add specific data / outcomes on the misuse / failure to use antibiotics in those cases of mal-adherence.

Conclusion was that a lot more attention and thought needs to be given to implementation. Although it is unclear where the weakness in implementation in the Responz study originates from.

4.3.3 *The qualities of the rapid GBS PCR test.*

E. Elzakker, microbiologist,

Most important outcome was thought to be the negative predictive value which in this case was 96.6 %. The rapid GBS PCR test would potentially solve some of the implementation issues. Previously the PCR test was still a complicated test and could only be carried out in the lab. The test has developed into a much simpler version which can possibly be carried out by non-lab technicians and at a 24 hours / day available point-of-care (POC).
Initially a lot of faulty tests turned up as, opposed to study guidelines, untrained staff was carrying out the test on the labour ward.
General Study results are good (see also page 29)

Running issues:

- Results cannot yet be coupled to Web based dossier (PWD) and are only available on paper.
- Test results susceptible to conditions of surrounding space (i.e. dust)
- Quality control (i.e. need to also send a culture to the lab).
- Untrained personnel (training needs to be repeated regularly to prevent new untrained staff using the equipment).

Based on the results of this study the expectation is that placing the equipment in the clinical lab (24/7) would be preferable. Experience from Utrecht Medical Centre, says that even with

equipment in micro-biology lab, 65% of tests are carried out in such a way that results are beneficial for management of GBS + clients.
Adherence to treatment on the basis of test results is 100%.
Paediatricians are also starting to request the rapid GBS PCR test.

Disadvantages:
Once test results are available and if they are negative, healthcare professionals may forget that other infections remain possible.
Currently the test is still expensive: Costs of the test (in the study) is euro 35.000 for PCR test apparatus, material / disposables for each test of euro 50,- and a maintenance contract of 4000,- / year. The expectation is that competition will be introduced into the market causing prices to drop.

4.3.4 Other remarks during the invitational Conference

- The role of the Health Inspectorate was also discussed. The Health Inspectorate will look at adherence to existing guidelines but won't act until it is obvious that care professionals fail to take up implementation (i.e. after five years).

- The Amsterdam Medical Centre (AMC) is currently doing research on virulent GBS strains and adapting treatment accordingly, as well as investigating maternal antibodies and contributing to global GBS vaccine development.

- Conclusion of this presentation and of participants is that introduction of rapid PCR test for GBS is timely and should be considered. This conclusion should be added to new NVK guideline.

- The issue is who's responsible for initiation of introduction of rapid PCR test for GBS .

- When GBS is discussed in regions, the microbiologists should be invited to participate.

- An implementation study of Rapid PCR for GBS should be undertaken.

4.3.5 Recommendations based on discussion

- Design a general infection prevention leaflet for parents
- Involve maternity care nurses during postnatal period (information & advice & alertness)
- Design an online tool to support care professionals (and parents?)
- GBS should become a theme in future Perinatal Audits.

5 Overall conclusion & recommendations

Adherence to EOGBS prevention management is poor regardless of strategy. If knowledge on the specifics of guidance (and the proposed strategy) remains low and uniformity in the utilization of guidelines is not achieved, prevention of EOGBS will not increase. At the same time it is important to realize that no strategy will prevent all cases of EOGBS and concerns remain over developing antibiotic resistance. It is therefore important to achieve a policy which aims to ensure the least possible numbers of women and their babies are exposed to antibiotics, while at the same time preventing the majority of EOGBS cases.

Care professionals are aware of the existence of the new concept guideline and expect that recommendations will be implemented in their region, once the guideline is approved by all professional organizations involved. The new guideline will answer the need for overall consistent policy and will give new impetus to the prevention of EOGBS. However, there is no reason to believe that the new guideline will improve adherence performance unless significant attention is given to implementation, concentrating on the following issues:

- This VIMP study has pointed out the importance of a clear and unambiguous description of recommendations with adequate definitions (see table 5 page 20),
- Specific attention to who is responsible for (communication of) results,
- Attention to communication with pregnant women, i.e. by developing an adequate information leaflet (see app.3) possibly supported by a web application,
- A multidisciplinary approach not only involving midwives, gynaecologists and paediatricians but also other (support) health care professionals such as O&G nurses and maternity care nurses.

Other possibilities that need to be investigated are the design of an online tool to support health professionals and parents. Furthermore, GBS should become a theme in future Perinatal Audits.

The PCR feasibility study undertaken in the Netherlands shows good results whereby the time-to-result is shortened considerably. However this test does require adequate training of personnel and attention to quality control as well as generating extra costs that must be put into balance with clinical benefits. One of the potential benefits is a reduction in the unnecessary administration of antibiotics. Although a cost-effectiveness study in daily practice should still be undertaken, the general consensus amongst experts is that the introduction of rapid PCR test for GBS is timely and should be considered. Another remaining issue is who is responsible for initiation of introduction of rapid PCR test for GBS. This could be solved by inviting the microbiologists to participate when EOGBS prevention policy is discussed locally.

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Appendix 1 Online Interview guide

1) Casus beschrijving voorleggen.
    a. Is casus duidelijk?
    b. Kunt u zich de casus goed herinneren?

2) Bij deze casus is op moment x van het protocol / de richtlijn afgeweken.

Wat waren volgens u de redenen/ overwegingen om in deze casus af te wijken van het beleid beschreven in het protocol?
Welke uitvoeringsproblemen kwam u tegen bij deze casus?
Welke zaken hebben te maken met uzelf?
Welke zaken hebben volgens u te maken met uw collega's / andere zorgverleners
Welke zaken hebben te maken met de client?
Welke zaken hebben te maken met de organisatie (in het ziekenhuis / in praktijk / in VSV / regio)

3) Afwijken van een protocol, indien goed onderbouwd, is niet verkeerd en kan onderdeel zijn van evidence based practice. Indien het protocol wel was gevolgd, denkt u dat de uitkomst van deze casus anders was geweest en waarom?

4) Welke aspecten van het GBS protocol heeft u als positief ervaren?
5) Welke aspecten van het GBS protocol heeft u als negatief ervaren?

NB kernelementen zoals hierboven

6) Hebben de zwangere en het kind volgens u de best mogelijke zorg ontvangen?

Tav GBS beleid In het algemeen
NB kernelementen
Zo ja / nee waarom wel / niet?

7) Was het van te voren duidelijk wat er van u werd verwacht mbt het beleid bij deze GBS casus?

Indien nee, waarom niet?
Steunvragen: bv beleid helder verwoord (volgorde / overzichtelijk / makkelijk te vinden)
Uw rol duidelijk
Staan er volgens u onjuistheden in
Ontbreken er zaken

8) Welke aspecten tav GBS protocol dienen volgens u te worden aangepast om implementatie te verbeteren?

NB kernelementen

9) Wat is er volgens u nodig om het GBS protocol beter in uw VSV / landelijk in te voeren en waarom?

Scholing
Extra tijd > zowel in VSV bespreking / consult tijd / voorbereiding (zoals lezen van protocol)
Betere afstemming met andere afdelingen / samenwerkingspartners
Heeft u suggesties voor ondersteunende instrumenten tbv implementatie die er voor zorgen dat het protocol beter gevolgd wordt en waarom?
Bv lijstjes / schema's / online tool

10) Heeft u nog overige vragen / opmerkingen of dingen die u aan ons kwijt wilt tav het GBS beleid / ondersteuning bij landelijke invoering?

Appendix 2 Overzicht van MIDI determinanten

Determinanten m.b.t. de innovatie

1 procedurele helderheid (o)
2 juistheid (o)
3 compleetheid (o)
4 complexiteit (o)
5 congruentie huidige werkwijze (o)
6 zichtbaarheid uitkomsten (o)
7 relevantie cliënt (o)

Determinanten m.b.t. de gebruiker

8 persoonlijk voordeel / nadeel (o)
9 uitkomstverwachting (o)
10 taakopvatting (o)
11 tevredenheid cliënt (o)
12 medewerking cliënt (e)
13 sociale steun (o)
14 descriptieve norm (o)
15 subjectieve norm (o)
16 eigen-effectiviteitsverwachting (o)
17 kennis (e)
18 informatieverwerking (o)

Determinanten m.b.t. de organisatie

19 formele bekrachtiging management (o)
20 vervanging bij personeelsverloop (o)
21 capaciteit / bezettingsgraad (e)
22 financiële middelen (e)
23 tijd (o)
24 beschikbaarheid materialen en voorzieningen (e)
25 coördinator (o)
26 turbulentie in de organisatie (p)
27 beschikbaarheid informatie over gebruik innovatie (o)
28 feedback aan gebruiker (o)

Determinanten m.b.t. sociaal politieke omgeving

29 wet- en regelgeving (e)

(o) op basis van objectieve (empirische) gegevens uit de gecombineerde data-sets
(e) op basis van theoretische verwachtingen van implementatiedeskundigen
(p) op basis van praktijkervaring van implementatiedeskundigen

Appendix 3 GBS cliënten Folder uit Responz onderzoek

Groep-B-streptokokken (GBS)
en zwangerschap

Groep-B-streptokokken (GBS) en zwangerschap
De groep B streptokok is een bacterie die bij veel zwangere vrouwen in de vagina aanwezig is. Dat kan meestal geen kwaad, maar een klein aantal baby's wordt ernstig ziek door een infectie met deze bacterie. In deze folder vindt u informatie over de groep-B-streptokokken ziekte en welke voorzorgsmaatregelen genomen kunnen worden om ziekte bij de baby te voorkomen.

Wat zijn de groep-B-streptokokken? Streptokokken zijn bacteriën. Ze zijn alleen zichtbaar onder de microscoop. Er zijn verschillende soorten streptokokken; de groep-B-streptokok is er een van en wordt meestal afgekort als **GBS**.

Hoe vaak komen GBS bij zwangere vrouwen voor? GBS komen voor bij één op de vijf zwangeren, zonder dat ze klachten veroorzaken. De GBS bevinden zich in de darmen. Ze zijn ook vaak in de vagina of baarmoedermond te vinden, zonder dat er klachten zijn. Soms kunnen ze een blaasontsteking veroorzaken. De GBS zijn dan in een kweek van de urine te vinden.

Hoe vaak komt GBS bij pasgeboren baby's voor? De helft van de moeders die GBS bij zich draagt geeft de bacterie door aan haar baby. In de meeste gevallen (99%) wordt de baby daar niet ziek van maar kan de 3

bacterie wel aangetoond worden bij de baby. Bij moeders die de GBS bacterie bij zich dragen wordt dus één op de honderd baby's ziek. Omdat niet alle moeders GBS bij zich dragen wordt van *alle* pasgeborenen uiteindelijk ongeveer **één op de duizend baby's ziek door een GBS-infectie.**

Hoe en wanneer krijgt de baby GBS bacterie van de moeder? Als een zwangere GBS bij zich draagt, kan dit overgedragen worden op de baby in de baarmoeder, tijdens de bevalling of na de geboorte.
 In de baarmoeder kan, zodra de vliezen zijn gebroken, de bacterie bij het vruchtwater komen en daardoor de baby bereiken. Dit kan heel soms ook als de vliezen nog niet gebroken zijn.
 In de vagina kan de bacterie worden overgedragen op de baby tijdens het persen.
 Na de geboorte kán de bacterie worden overgedragen op de baby in de eerste dagen of in de eerste weken. De kans hierop is heel erg klein. Meestal wordt de bacterie dan via de

handen van een volwassene overgedragen op de baby (dit hoeft niet de moeder te zijn). Het is belangrijk goed de handen te wassen voordat iemand de baby oppakt.

GBS infectie bij de baby Als een baby ziek wordt door een infectie met GBS, is dat in negen van de tien gevallen op de eerste dag. De baby ademt vaak snel en oppervlakkig. De kleur van de huid is grauw, blauw of bleek. De baby kan slap aanvoelen en suf zijn. Een zacht kreunend geluid bij het uitademen is vaak het eerste verschijnsel van de GBS-ziekte. Het kreunende geluid is een belangrijk waarschuwingssignaal, maar ook een snelle ademhaling of een afwijkende kleur kunnen signalen zijn van GBS-ziekte. Problemen met voeding zoals spugen of niet willen drinken, koorts of juist een te lage temperatuur kunnen soms ook een teken zijn van GBS-ziekte.
De infectie kán ernstig verlopen. Zieke baby's moeten dan ook altijd in het ziekenhuis met antibiotica worden behandeld. De behandeling met antibiotica is meestal effectief.

Wanneer hebben baby's een verhoogde kans op een GBS-infectie?
Van een aantal risicofactoren tijdens de zwangerschap of bevalling is bekend dat dan de kans hoger is dat de baby de GBS bacterie overgedragen krijgt:

- Als de vliezen langdurig gebroken zijn (langer dan 18-24 uur);
- Als de baby te vroeg geboren wordt (voor 37 weken zwangerschap);
- Als de moeder koorts heeft tijdens de bevalling (meer dan 38,0°C);
- Als de moeder in de zwangerschap een blaasontsteking heeft gehad door GBS;
- Als de moeder een eerder kind met GBS-infectie heeft gehad.

Hoe kan een GBS-infectie bij de baby voorkomen worden? Als er tijdens de bevalling antibiotica wordt gegeven aan de moeder kan voorkomen worden dat de baby ziek wordt. Het is echter lang niet altijd mogelijk om een GBS-infectie te voorkomen.
De richtlijn van gynaecologen en kinderartsen in Nederland is dat moeders antibiotica tijdens de bevalling krijgen:

- Als de moeder koorts heeft tijdens de bevalling (meer dan 38,0°C);
- Als de moeder in de zwangerschap een blaasontsteking heeft gehad door GBS;
- Als de moeder een eerder kind met GBS-infectie heeft gehad.

Bij zwangeren waarbij

- de vliezen langdurig gebroken zijn of
- de bevalling voor 37 weken plaats vindt.

wordt niet automatisch gestart met antibiotica maar wordt eerst een kweek afgenomen bij de moeder via de vagina en anus. De uitslag van die kweek 6 duurt soms erg lang. Dan besluit de behandelend gynaecoloog of er gestart wordt met antibiotica

Als een van de bovenstaande risicofactoren aanwezig was bij de bevalling, wordt de baby opgenomen ter observatie.
De baby wordt de eerste 48 uur extra in de gaten gehouden als u

- eerder een kind met GBS-ziekte had
- een blaasontsteking in de zwangerschap door de GBS bacterie had
- lang gebroken vliezen zonder weeën had

Van deze 48 uur wordt de baby de eerste 24 uur in het ziekenhuis in de gaten gehouden. Als de baby na 24 uur geen symptomen van infectie heeft, mag de baby mee naar huis.
Als de moeder koorts heeft gehad tijdens de bevalling of als de gynaecoloog of kinderarts denkt dat er een infectie bij de baby is, wordt bij de baby bloed afgenomen en een kweek gedaan. De baby krijgt dan ook antibiotica per infuus.

Wat is het nadeel van antibiotica tijdens de bevalling?
De antibiotica wordt via een infuus gegeven aan de moeder tijdens de bevalling. Dat betekent dat u in het ziekenhuis moet bevallen en tijdens de bevalling vast zit aan de infuuslijnen. Antibioticagebruik kan namelijk bij sommige mensen leiden tot een shock. Dit is weliswaar een ernstige maar ook zéér zeldzame complicatie. Dit komt voor bij ongeveer 1 op de honderdduizend vrouwen.
Bij teveel antibiotica gebruik is er altijd een risico dat de bacterie uiteindelijk ongevoelig wordt waardoor de antibiotica niet meer werkt. Bij de antibiotica die bij GBS wordt gebruikt (penicilline) is dat nog niet het geval. Er zijn echter mensen die niet tegen penicilline kunnen. Dan worden er andere antibiotica gebruikt. Voor een van deze antibiotica (amoxicilline) is de bacterie wel al ongevoelig aan het worden.

Meer informatie
Wilt u meer informatie nalezen over GBS infectie en preventie van een GBS infectie, kunt u zich richten tot:

- De Stichting GBS, Trekweg 58, 7322 HS Apeldoorn;
- Stichting Ouders Groep B Streptokokken Patiënten, www.ogbs.nl.

Appendix 4 Program Invitational Conference

13 April 2017

Invitational conference EOGBS beleid in Nederland
Early onset Groep B- hemolytische streptokokken infectie (EOGBS) is een belangrijke oorzaak van neonatale morbiditeit en mortaliteit tijdens de eerste levens week. Er zijn verschillende strategieën bekend om de preventie van EOGBS te bevorderen.
In Nederland wordt tot op heden een aangepast beleid gevoerd waarbij niet gescreend wordt op GBS, maar waarbij hoog risico zwangeren tijdens de partus gekweekt worden. Onderzoek van TNO laat zien dat de implementatie van GBS beleid, ongeacht de strategie, nog veel te wensen overlaat. Onder leiding van de Nederlandse Vereniging van Kinderartsen (NVK), in samenwerking met de Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG) en de Koninklijke Organisatie voor Verloskundigen (KNOV), kwam recent een nieuwe richtlijn Preventie en behandeling van early-onset neonatale infecties, waar onder EOGBS, tot stand (laatste revisie in februari 2017).
Om tot een goede afstemming te komen over de betekenis van recente studieresultaten, de meest optimale EOGBS preventie strategie en gezamenlijke afspraken over de implementatie wordt in de middag van 13 april 2017 een invitational conference gehouden met alle stakeholders.

Doelstelling:

- Het vaststellen van de best haalbare gezamenlijke preventie strategie voor EOGBS
- Het komen tot gezamenlijke afspraken voor de implementatie van het afgesproken beleid
- Afspraken maken rondom de eventuele invoering van de PCR-test, beter bekend als de sneltest, voor de diagnostiek van GBS-dragerschap.

Locatie:
TNO, Gebouw 1, Vergaderruimte 1.1.07 + 1.1.08
Utrechtseweg 48, 3704 HE Zeist
Telefoon:088 866 6000
Bereikbaar met bus 50 of 51 vanaf Utrecht CS

Accreditatie wordt aangevraagd voor KNOV / NVOG / VKN / Microbiologen / V&VN / Kraamzorg.

Start 14.00

- Opening

Middag-voorzitter Maurice Wouters, gynaecoloog, VUmc te Amsterdam

- Overzicht GBS in Nederland en presentatie nieuwe richtlijn

René Kornelisse, neonatoloog, EMC te Rotterdam

- Resultaten TNO & VUmc onderzoek implementatie EOGBS-strategieën

Diny Kolkman, promovendus en verloskundige, MCA te Alkmaar

- Stand van Zaken GBS-Sneltest

Erika v Elzakker, microbioloog,

HAGA ziekenhuis te Den Haag

- Discussie met de zaal aan de hand van stellingen
- Afsluiting door voorzitter
- +/- 16.30: Borrel

Genodigden: vertegenwoordigers van de samenwerkende beroepsorganisaties (KNOV, NVK, NVOG, NHG, V&VN, NBVK), microbiologen, cliëntvertegenwoordigers (GBS patiënten vereniging, NPCF, Geboortebeweging, Zelfbewust Zwanger), verzekeraars, IGZ, ZonMW, CPZ, VWS.

Appendix 5 Summary of available EOGBS guidelines

Country	Year	Organization / Entity	Title & Type	GBS recommendations	Remarks
Netherlands	2008	NVOG	Preventie van neonatale groep-B-streptok Guideline	No screening Identification of risk factors Cultures during labour IAP: when GBS is confirmed / previous child with EOGBS / maternal fever during labour Observation neonate after treatment IAP. Diagnostics and treatment if sepsis is confirmed.	Risk factors prem birth & PROM are most prevalent. (NSCK, 1997-1998). In daily practice a cut-off point / time of 24 hrs after PROM is used (VIL 2003, TTM 2017)
Netherlands	2017	NVK	Preventie en behandeling van early-onset neonatale infecties (Adaptation of NICE-guideline)	Indication for determination of GBS status: -(threatened) prem birth -PROM > 24 hrs No standardised screening. But advices to discuss determination of GBS status between 35-37 weeks with pregnant women when: -GBS colonisation was present in a previous pregnancy - a previous child was treated for early onset neonatal septicaemia or meningitis caused by unknown organism and respiratory or circulatory support was necessary. Strategy based on the identification of “red flags” IAP when: *Confirmed GBS colonization (positive urine and / or recto-vaginal culture) in current pregnancy. *Previous child with GBS disease *Consider IAP when PROM occurs <37 weeks of pregnancy and GBS status is unknown.	The guideline encourages the use of the rapid PCR test: Use PCR test for GBS if available when risk factors are present.

Country	Year	Organization / Entity	Title & Type	GBS recommendations	Remarks
UK	2012	NICE	• Guideline • Neonatal infection (early onset): antibiotics for prevention and treatment CG149	Use the framework based on risk factors and clinical indicators, including red flags to direct antibiotic management decisions. IAP for women with: -a previous baby with an invasive group B streptococcal infection -group B streptococcal colonisation, bacteriuria or infection in the current pregnancy. - in preterm labour if there is prelabour rupture of membranes of any duration. -in preterm labour if there is suspected or confirmed intrapartum rupture of membranes lasting more than 18 hours. Do not routinely give antibiotic treatment to babies without risk factors for infection or clinical indicators or labouratory evidence of possible infection.	
UK	2012	RCOG	Green top guideline no.36: The Prevention of Early-onset Neonatal Group B Streptococcal Disease	Routine bacteriological screening of all pregnant women for antenatal GBS carriage is not recommended since it is not supported by current evidence. IAP on the basis of risk factors. Current evidence does not support the administration of IAP to women in whom GBS carriage was detected in a previous pregnancy. Well infants at risk should be observed for first 12–24 hours after birth with regular assessments of general wellbeing, feeding, heart rate, respiratory rate and temperature	

Country	Year	Organization / Entity	Title & Type	GBS recommendations	Remarks
UK	2016 New text proposal (consultation ends jan 25 2017)	NSC	Recommendation on Group B Streptococcus screening in pregnancy (currently, in consultation)	Screening for GBS should not be offered to all pregnant women. - insufficient evidence to demonstrate that the benefits to be gained from screening all pregnant women and treating those carrying the organism with intravenous antibiotics during labour would outweigh the harms.	Systematic reviews of culture testing suggest that many screen positive women may no longer be carriers at the point of treatment. In the absence of a diagnostic test, current screening strategies are unable to distinguish between carriers whose babies will be affected by early onset GBS and those which would not. As a result many thousands of low risk women would receive intravenous antibiotic prophylaxis during labour. The consequences of expanding antibiotic usage in this way are unknown.
Canada	2013	SOCG	Clinical Practice guideline no 298 The Prevention of Early-Onset Neonatal Group B Streptococcal Disease	Screen all women at 35-37 weeks (recto-vaginal swab) IAP given to: all women with + screentest; -all women with history of sick GBS infant; -all women with documented GBS-UTI; -all women in prem. Labour or with prem. ROM unless screen was neg within previous 5 weeks; -women in labour with fever; SROM with risk factor or +screen.	
US	2010	CDC		Universal screening between week 35-37 IAP for: Women with confirmed colonisation Previous child with EOGBS (regardless of screening) All women with a + screening test If test results not available: IAP for women in prem labour, PROM > 18 hrs, Temp > 38	

Country	Year	Organization / Entity	Title & Type	GBS recommendations	Remarks
New Zealand / Australia	2014	Multidiscipliniary	The prevention of early-onset neonatal group B streptococcus infection: Consensus Guideline	Risk-based GBS prevention strategy IAP for: a. a previous GBS-infected baby b. GBS bacteriuria of any count during the current pregnancy c. preterm (<37 weeks) labour and imminent birth d. intrapartum fever ≥ 38 C e. membrane rupture ≥ 18 hours An incidental finding alone does not require treatment antenatally	
New Zealand	2016	RANZCOG	Disclosure statement	Intrapartum antibiotic prophylaxis with IV penicillin-G or ampicillin offered to all women at increased risk: Spontaneous onset of labour at ≤ 37 weeks gestation. Rupture of membrane ≥ 18 hours. Maternal fever ≥ 38°C. A previous infant with EOGBS. GBS bacteruria during the current pregnancy. Known carriage of GBS in current pregnancy. Clinical diagnosis of chorioamnionitis Other twin with current EOGBS.	Universal culture-based screening, using combined low vaginal plus or minus anorectal swab at 35-37 weeks gestation, or a clinical-risk factor based approach are both acceptable strategies for reducing EOGBS.
Belgium	2004	VWV / VVOG:	Disclosure statement (Standpunt) Prevention of Group B streptococcus infections & pregnancy	IAP for screen pos women, women with GBS urine infection this pregnancy and women with previous child with EOGBS	Guideline / disclosure statement of Belgium Paediatricians not available for public.

Appendix 6 Available literature on rapid PCR-based test for detection of GBS

Name / publication / country / year	Type	Methods	Results	Remarks
Bjorklund, 2016, Finland (PCR) (47)	• Evaluation of the effect of a rapid PCR-based group B streptococcus (GBS) test on length of stay in hospital among newborns, antibiotic use, and GBS-early-onset-disease (EOD) incidence.	• A before and after service evaluation including term deliveries between 1st January and 12th November 2014 (6688 deliveries). • Length of stay in the hospital, GBS-EOD incidence and antibiotic use were evaluated.	• Three confirmed and 74 possible cases of GBS-EOD were found in Phase 1, and 85 possible cases in Phase 2. • In newborns with suspected infection, the introduction of the rapid test was related to a decreased length of stay on the pediatric care unit by 1.16 days ($p = 0.01$), and an increase in the length of stay on the mother-and-baby ward by 1.11 days ($p < 0.001$). No increase in antibiotics was noted.	• CONCLUSION: The introduction of a point of care test was associated with a reduction in length of stay in the paediatric care unit, without an increase in antibiotic use. This test could improve the accuracy of GBS colonization detection, and help to prevent intrapartum transmission as no verified GBS-EOD cases were recorded with the intrapartum PCR algorithm.
El Helali, France, 2012 (19)	Cost effectiveness study of systematic intrapartum vagina PCR screening for term deliveries	Comparing the intrapartum PCR screening strategy implemented in 2010 with antenatal culture strategy during pregnancy in place in 2009. Early-onset GBS disease in newborns was monitored exhaustively. Direct costs estimated, including screening test costs and hospital costs, for births of healthy newborns compared with those infected with GBS. Costs in 2009 and 2010 were compared on an	Term deliveries were 2,761 and 2,814 in 2009 and 2010, respectively. Among the screened mothers, the vaginal GBS colonization rate was 11.7% based on antenatal GBS culture screening in 2009 compared with 16.7% in 2010 using the intrapartum PCR testing. The overall probabilities of neonatal GBS disease were 0.9% compared with 0.5%, and the average total cost per delivery was $1,759_1,209 in 2009 compared with $1,754_842 in	In 2009 IAP administered if AN screening was positive or in case of bacteriuria during current pregnancy or a previous child with EOGBS disease. If GBS status unknown at time of birth, a risk-factor assessment (eg, PROM > 12 hours, intrapartum fever > 38°C) is used to determine whether IAP should be administered In 2010 intrapartum PCR screening strategy, IAP when screened positive, to those presenting obstetrical risk factors when samples did not give

Name / publication / country / year	Type	Methods	Results	Remarks
		intention-to-treat basis.	2010 (*P*_.9) in antenatal and intrapartum screening strategies, respectively. The number and severity of cases of early-onset GBS disease and the resulting hospital costs were higher in 2009.	PCR result (eg, PCR invalid or error), and to mothers with history of EOGBS. IAP is not indicated when: negative intrapartum screening result, absence of obstetrical risk factors, sample did not give a PCR result, and positive screening in a previous pregnancy.
Elzakker, Congress poster, Netherlands / 2014 (40)	Feasability study with GBS-PCR test (Xpert GBS test)	Comparing performance of PCR with standard cultures with vaginal-rectal swabs from women in preterm labour and or with PROM Also comparing performance of PCR in lab against PCR at point of care (POC)	Swabs from 306 women. 283 eligible for further analysis. 22,3% of cultures were + PCR in Lab : Sens 96,5% Spec 89,3% PPV 72,1% NPV 98,9% PCR at POC : Sens 88,2% Spec 94,2% PPV 81,1% NPV 96,6% Median time to result reduced from 70,4 hrs to 1,5 hrs Initial invalid test rate at POC was 26,6 compared to 3% in lab. But at POC this was reduced to 6,8% after simplification of test by manufacturer.	Xpert GBS test performs well and can be implemented at POC providing adequate training and supervision. Added info in personal communication : Preferable POC is clin. Chem. (available 24/7) as training is easier. Costs are high : reactive agents 45/50,- & Machine 15-20.000. Home swabbing should be possible as time etc does not affect quality of results.
Hakansson etal, Sweden 2014 (41)	RCT	Comparing performance of PCR with standard cultures with vaginal-rectal swabs from women in labour with a risk factor (PROM, Prem birth, GBS-uria this pregnancy.	N=229 (112 vs 117) Phase 1 : 44% of PCR inconclusive. After improvement test 15% (P<0.001) Sens 89%, Spec 90% (when PCR was conclusive.)	Author's conclusion : PCR used on labour ward is feasible albeit the management in the hands of midwives and assistants could be further improved. In this study also manufacturers

Name / publication / country / year	Type	Methods	Results	Remarks
		Women with previous GBS child were excluded. 2 phases : phase 2 was with improved PCR. Randomisation by clustered envelopes. Blinding ? Inlc women with riskfactors prem birth >34 <37 PROM 18 hrs GBS bacteriuria this pregnancy Excluding : Prem birth < 34 Penicillin intollerance Previous child with EOGBS	Phase 1+ 2 combined (conclusive tests) : Sens 87% Spec 95% PPV 92% NPV 92% In phase 2 94% of women with + PCR were given IAP. 33% of all women in phase 2 were given IAP.	refinement as in Elzakkers study. El Helali etal used this same latest version of test with 9% of the results being indeterminate. Authors also suggest that the more experienced with the test the less indeterminate results
Mueller etal Switserland, 2014 (42)	Prospective cohort study	All women >24 weeks at onset of labour. Women with elective CS and no contra-indication for VE were also included. Inclusion period Jan 2007-aug 2010. Phase 1 N=150 2 VR-swabs per woman > both processed in lab (PCR and culture). Phase 2 N=150 PCR test performed on labour ward by attending obstetrician or midwife, 2nd swab sent to lab for culture.	N=300 Mean age 29.7 Mean gest age 33 wks GBS colonisation rate 18.6% by both PCR and culture. Phase 1 N=150 24 tests positive by both PCR & culture (true positive) 117 samples negative on both tetsts (true positive) 4 positive culture, neg on PCR (false neg) 5 positive on PCR, neg on culture (false pos) Sens of PCR compared with culture 85.7% (95% CI 68.5-94.3) Spec 95.9% (95% CI 90.8-98.2) PPV 82.76% NPV 96.69%	Training improved quality of test results. No risk factors considered.

Name / publication / country / year	Type	Methods	Results	Remarks
			Pos likelihood 20.91 Neg Likelihood 0.149 Diagnostic accuracy reached 94% 8.5% of PCRs were invalid. Phase 2 N=150mean age 29.7 Mean gest age 36 weeks GBS colonisation rate 23.3% True pos rate 30 True neg rate 110 5 false pos 5 false neg Sens 85.71% (95% CI 70.6-93.7) Spec 95.66 (95% CI 90.2-98.1) PPV 85.71% NPV 95.65% +likelihood 19.71 -likelihood 0.149 Diagn accuracy 93% 23.5% of PCR swabs were invalid	