Antibiotic stewardship bij neonatale infecties: veiligheid en effectiviteit van orale amoxicilline/clavulaanzuur

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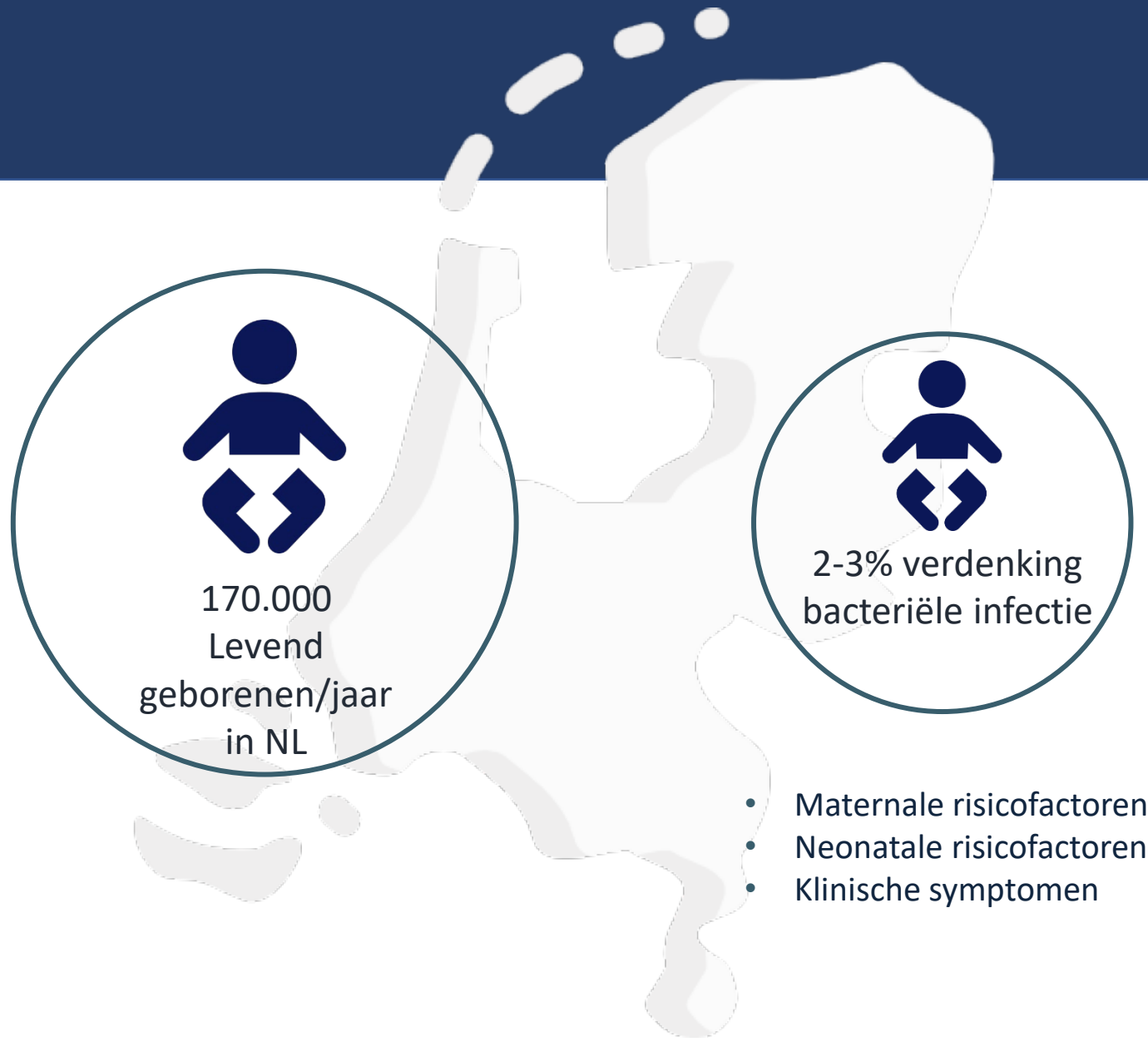
Disclosures

Geen potentiële belangenverstrengeling

Geen voor bijeenkomst mogelijk

relevante relaties met bedrijven

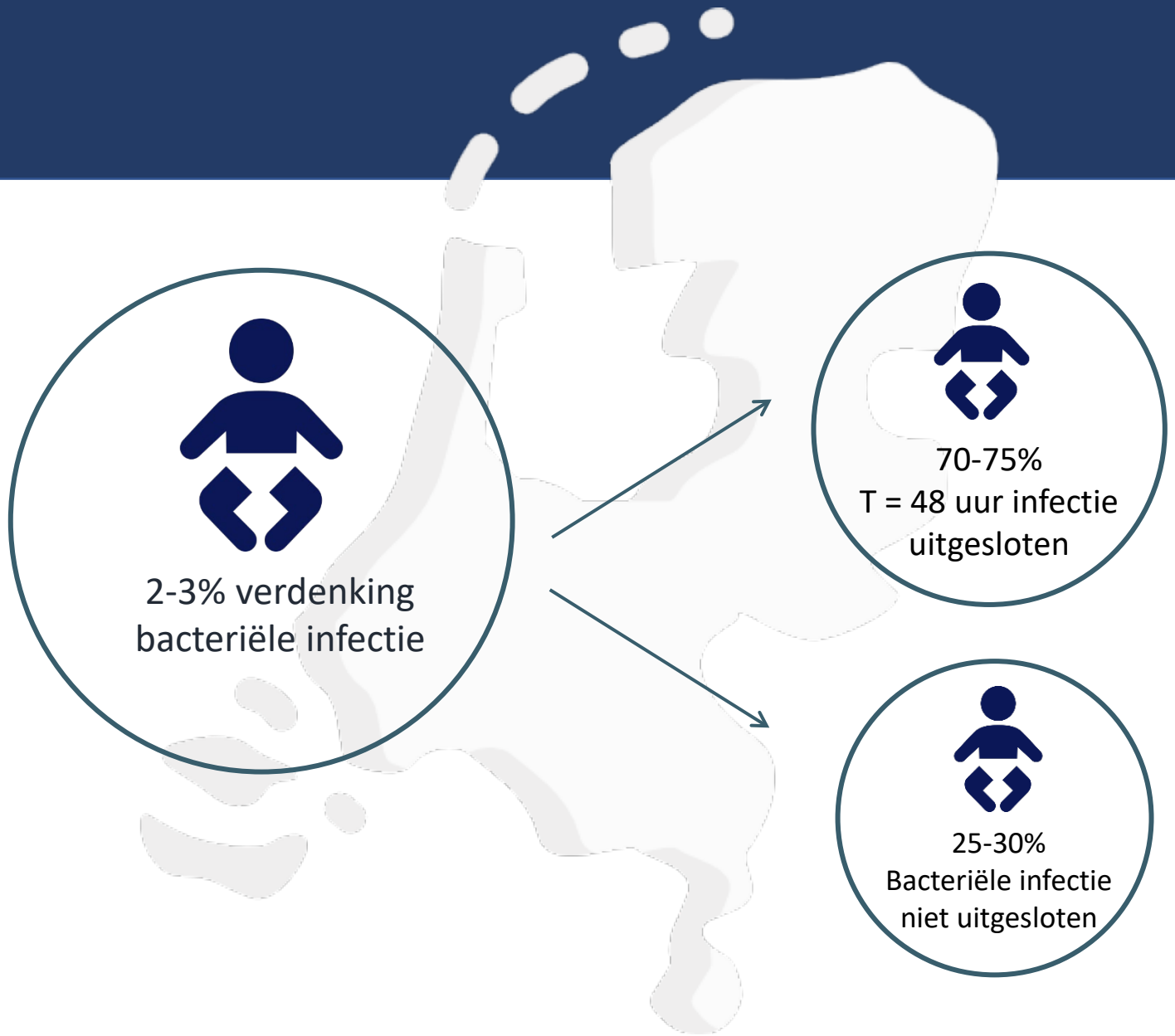


170.000
Levend
geborenen/jaar
in NL

2-3% verdenking
bacteriële infectie

- Maternale risicofactoren
- Neonatale risicofactoren
- Klinische symptomen

Bron: Perined 2018-2021



Bron: Perined 2018-2021

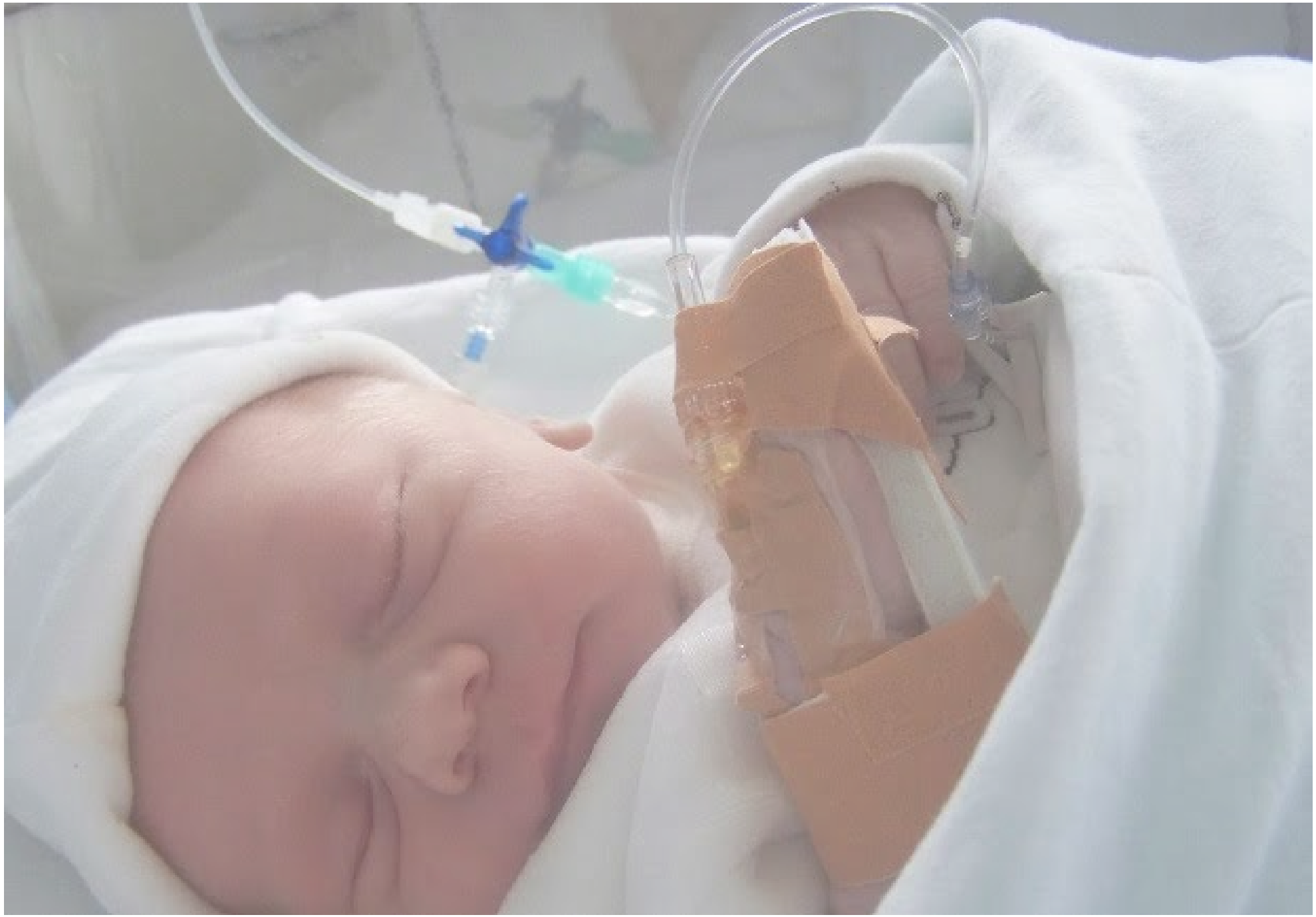


Table 1. Principles and Strategies for AS Programs

Principles	Examples of Strategies
Timely antibiotic therapy management	Ensuring prompt initiation of antibiotic therapy when indicated Critical illness such as sepsis High-risk patients with serious bacterial infections Avoiding use of antibiotics when not indicated Viral upper or lower respiratory tract infections Asthma exacerbations Viral pharyngitis Use of clinical guidelines and algorithms that facilitate provider recognition of clinical syndromes that do and do not require antibiotics
Appropriate selection of antibiotics	Ensuring that proper antibiotic regimens are selected for specific clinical syndromes and infections Minimizing redundant antibiotic regimens for gram-negative or anaerobic bacterial infections Use of antibiograms and clinical guidelines to optimize antibiotic selections
Appropriate administration and de-escalation of antibiotic therapy	Ensuring proper dosing of antibiotics Peer review of antibiotic use at 48-72 h after initiation to determine if therapy should be continued, changed, or discontinued Monitoring for serum therapeutic levels of antibiotics Proper administration of antibiotics for surgical prophylaxis
Use of expertise and resources at point of care	Formation of multidisciplinary AS committees Obtaining administrative and leadership support
Continuous and transparent monitoring of antibiotic use	Auditing antibiotic use to identify opportunities for stewardship and education Prospective monitoring to assess efficacy of AS program

Abbreviation: AS, antimicrobial stewardship.

JAMA Pediatr. 2013;167(9):859-866. doi:10.1001/jamapediatrics.2013.2241

Bestaande evidence

J Antimicrob Chemother
doi:10.1093/jac/dkz252

Journal of Antimicrobial Chemotherapy

Oral antibiotics for neonatal infections: a systematic review and meta-analysis

Fleur M. Keij[1,2]*, René F. Kornelisse[1], Nico G. Hartwig[2], Irwin K. M. Reiss[1], Karel Allegaert[1,3] and Gerdien A. Tramper-Stranders[1,2]

RAIN

Reduction of intravenous
Antibiotics In Neonates

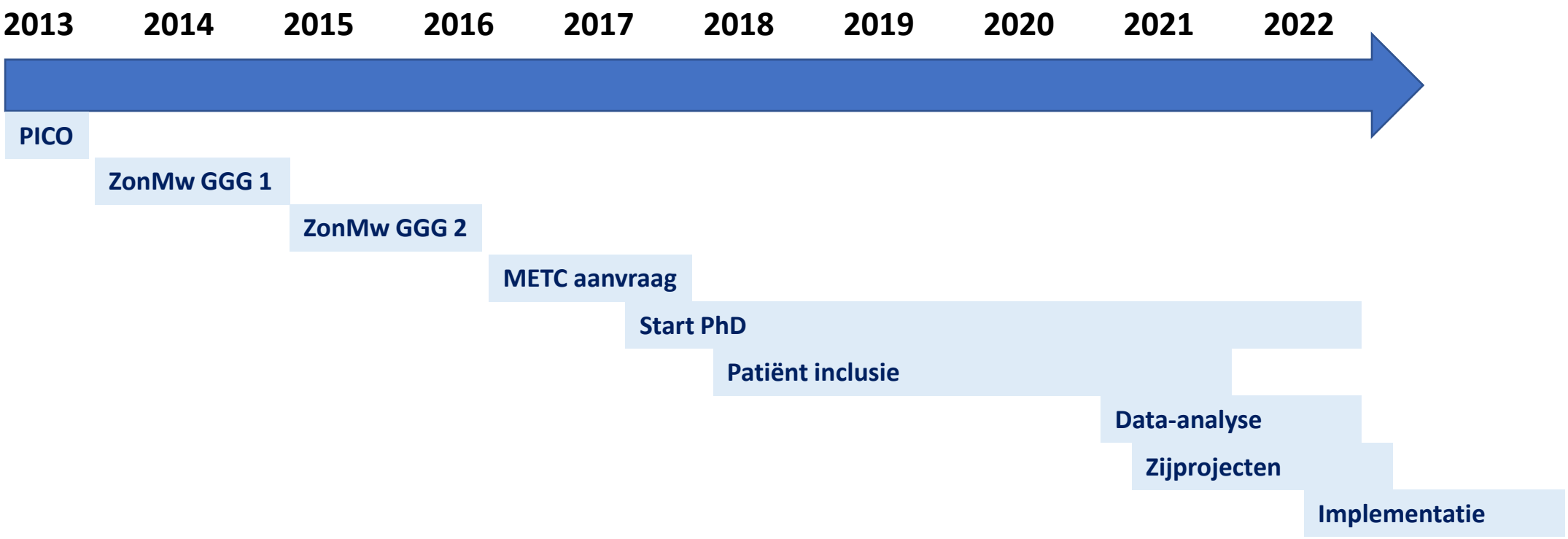
PRIMAIRE DOELSTELLING

Aantonen van non-inferioriteit van iv-orale switch therapie

bij klinisch stabiele neonaten

met een waarschijnlijke bacteriële infectie

RAIN | tijdslijn studie



17 ziekenhuizen

17 uitdagingen

- **Offertes**
- **Contracten**
- **Indieningsprocedures**
- **Duur tot > 6 maanden**

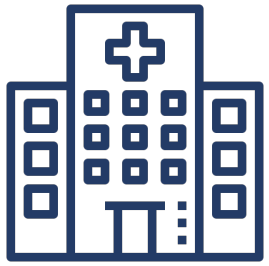
510 pasgeborenen

17 ziekenhuizen

02-2018 t/m 06-2021

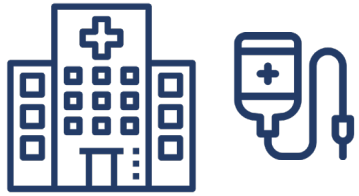
RAIN | studieopzet

≥ 35 weken
≥ 2 kg
1ste levensmaand
Waarschijnlijke bacteriële infectie waarvoor uitbehandeling met antibiotica geïndiceerd is



NA 36-48 UUR

Amoxicilline/clavulaanzuur
75 mg/kg/dag tid



Standaard protocol

RAIN | primaire uitkomstmaat

PRIMAIRE UITKOMSTMAAT

- Bacteriële (re)-infectie binnen 28 dagen

SECUNDAIRE UITKOMSTMATEN

- Adverse events & bijwerkingen
- Opnameduur
- Farmacokinetiek
- Kwaliteit van leven & kosten-effectiviteit
- Microbioom in het eerste levensjaar
- Pathogeen detectiemethoden


BETTER
WORSE
3 PROCENT

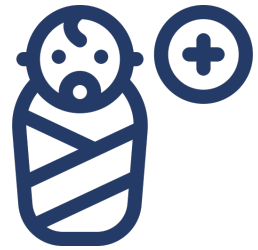
RAIN | baseline

58 % man

40+0 weken

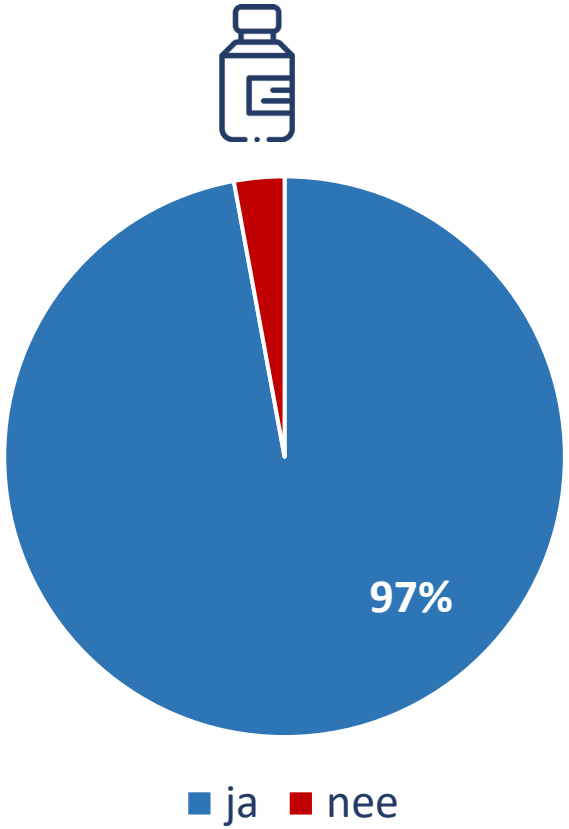
3614 gram

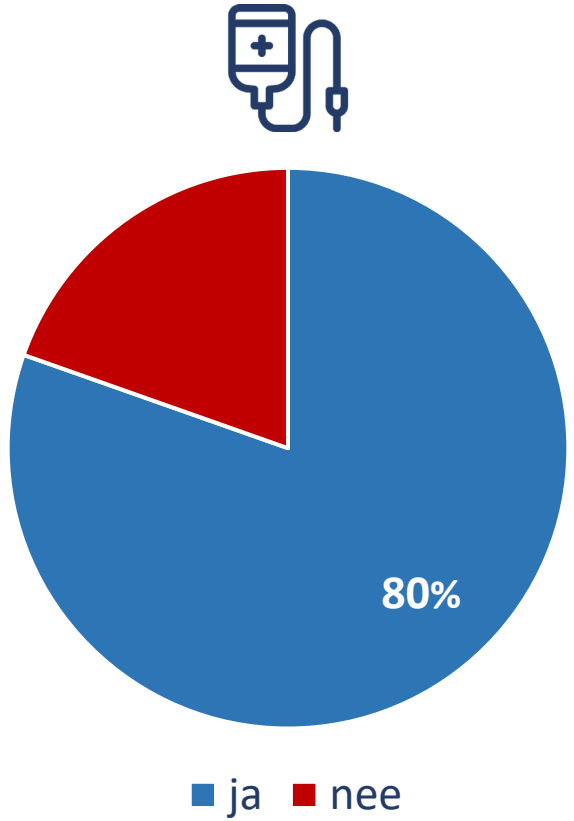
31.6% langdurig gebroken vliezen
45.5% maternale koorts
28.5% verdenking maternale sepsis waarvoor antibiotica



83.4% klinische symptomen

RAIN | behandeling afgerond?





RAIN | primaire uitkomstmaat

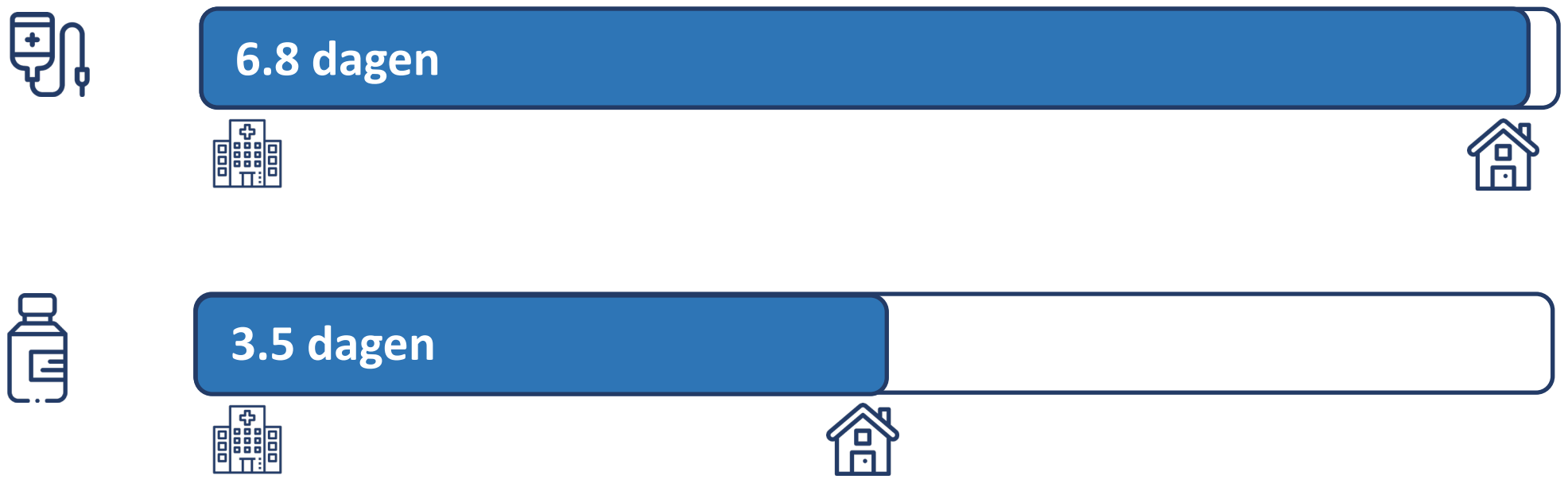
(Re)infectie rate

n = 1 (0.4%)

n = 1 (0.4%)

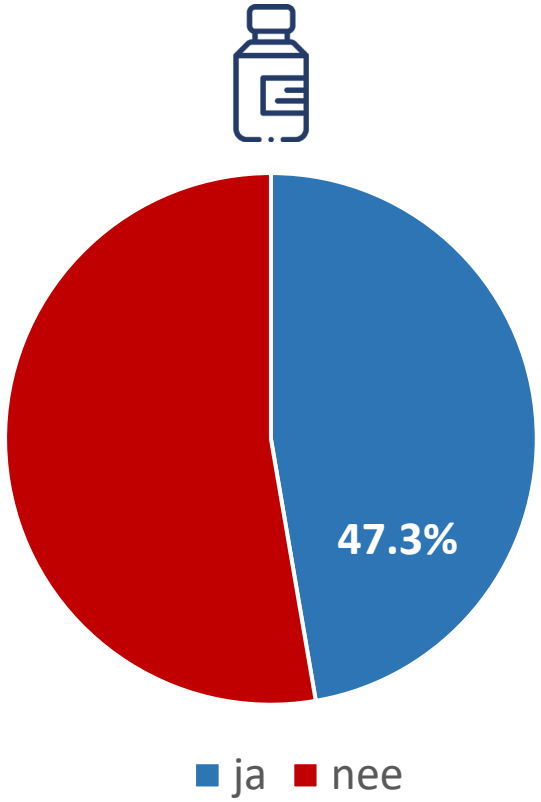
IV-orale switch niet inferieur aan volledige infuusbehandeling

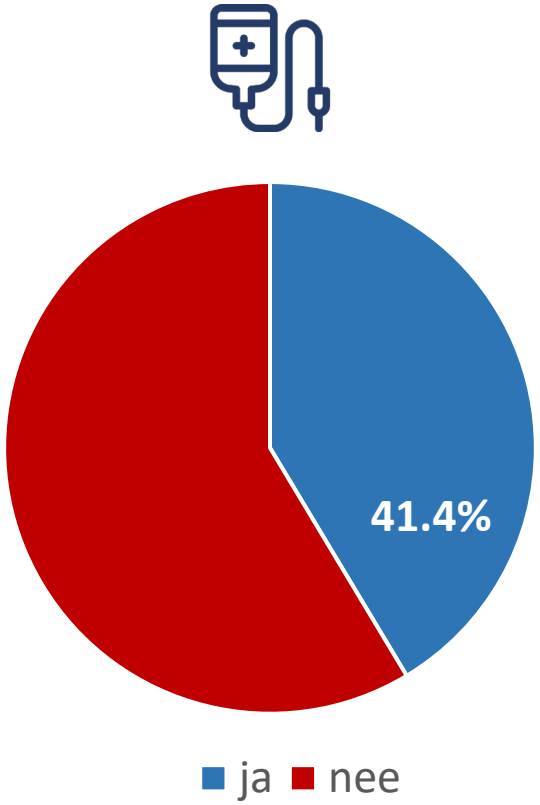
RAIN | mediane opnameduur



Significante reductie in opnameduur

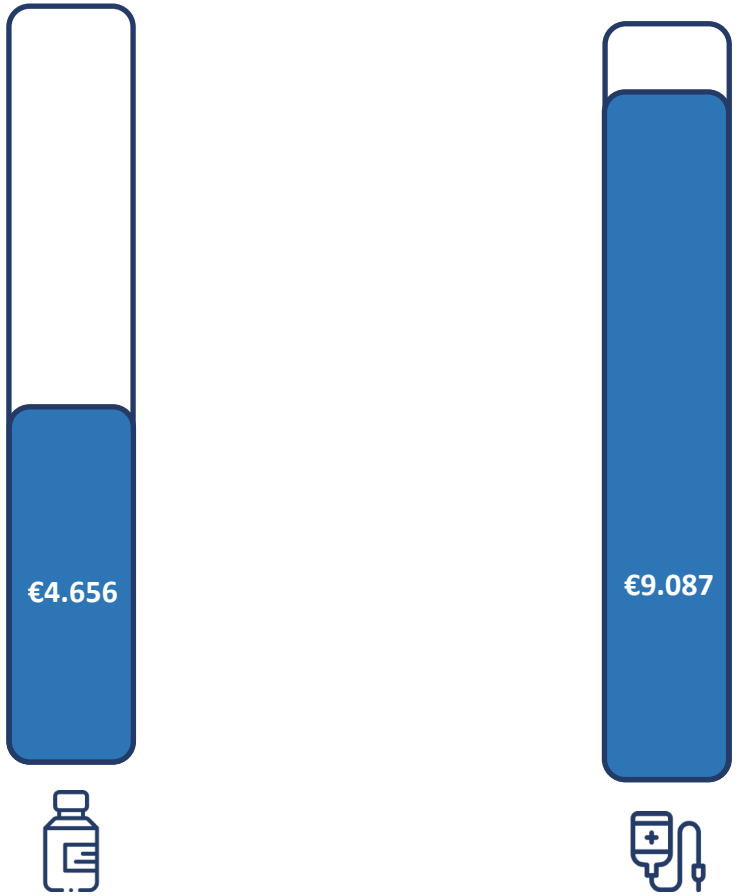
RAIN | bijwerkingen





Niet significant meer bijwerkingen

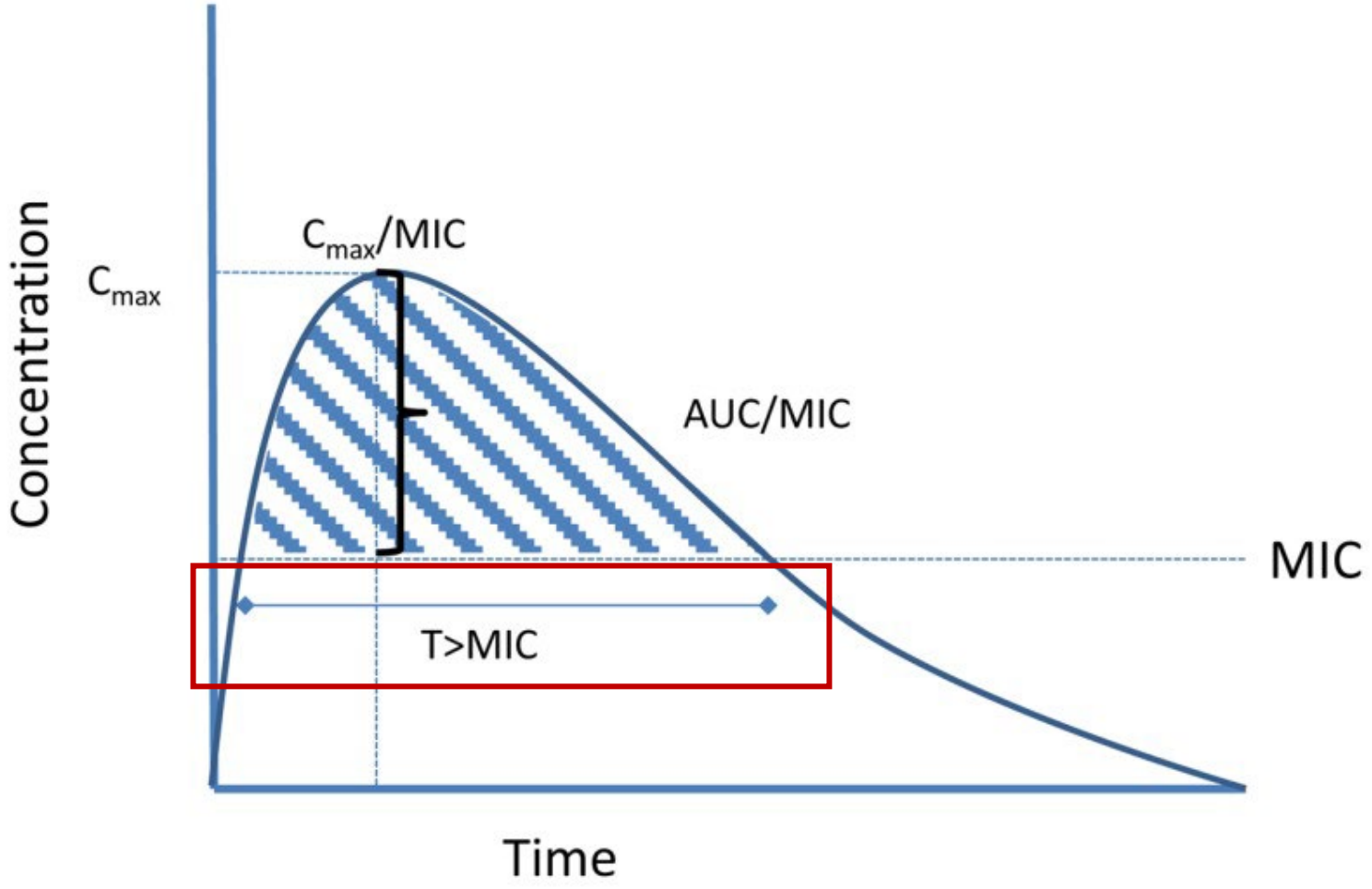
RAIN | totale opnamekosten



1.105 * 4.431 = 4.9 miljoen euro/jaar

Significante reductie in zorgkosten

RAIN studie | farmacokinetiek



RAIN studie | farmacokinetiek

MIC = Minimal Inhibitory Concentration

GBS: 0.25 mg/L

E. Coli: 8 mg/L

<u>Pasgeborenen: tijd > MIC minimaal 50%</u>

RAIN | farmacokinetiek

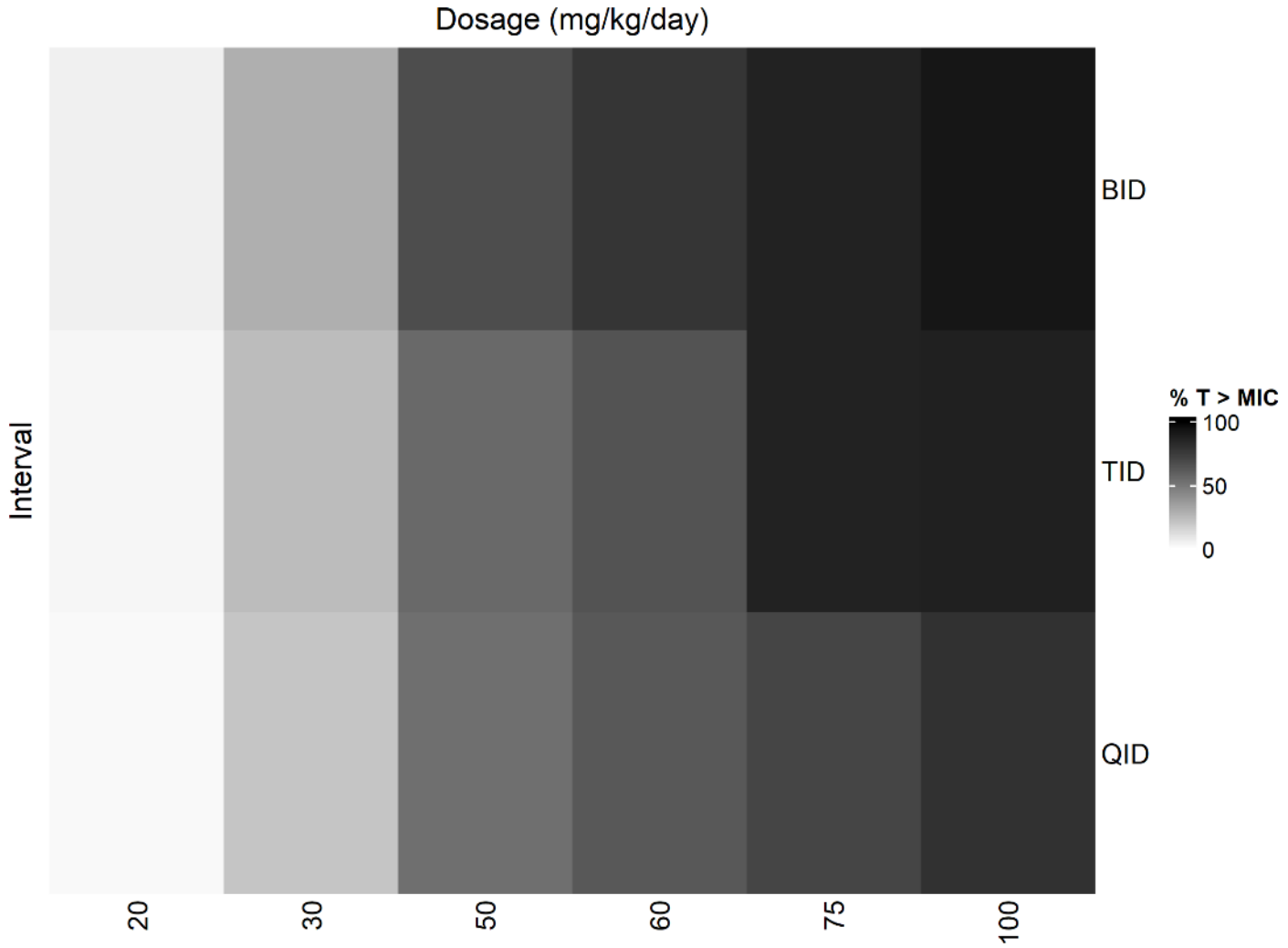
% T>MIC (0 – 24h)

	% T>MIC (0 – 24h)		
mg/kg/day	**BID**	**TID**	**QID**
20	5.2	3.1	2.2
30	28.4	23.7	20.5
50	67.3	55.6	53.4
60	78.0	64.8	62.8
75	87.0	86.9	70.6
100	92.9	87.5	79.7

BID: twee maal daags

TID: drie maal daags

QID: vier maal daags



RAIN | Zijstudies & spin-of

KORTE TERMIJN

Amoxicilline en clavulaanzuur farmacokinetiek

Moleculaire typering van negatieve bloedkweken

Darm microbioom ontwikkeling 1e levensjaar

LANGE TERMIJN

Cohort vervolgen in kindertijd

Verdere samenwerking deelnemende ziekenhuizen voor andere/nieuwe projecten

Conclusie

Iv-orale switch therapie is niet inferieur aan iv antibiotica bij neonaten met een waarschijnlijke infectie

Het gebruik van orale antibiotica is niet geassocieerd met meer bijwerkingen

Het gebruik van orale antibiotica leidt tot een reductie in opnameduur van 3.5 dag

De gebruikte dosering van 75 mg/kg/dag in drie doseringen leidt tot (meer dan) adequate blootstelling

▲ Hoewel het meestal snel weer goed gaat, moeten de baby'tjes toch een week in het ziekenhuis blijven om de kuur af te maken. © Thinkstock

Waarschijnlijk op korte termijn

Pasgeboren baby'tje bij infectie eerder naar huis

Implementatietraject

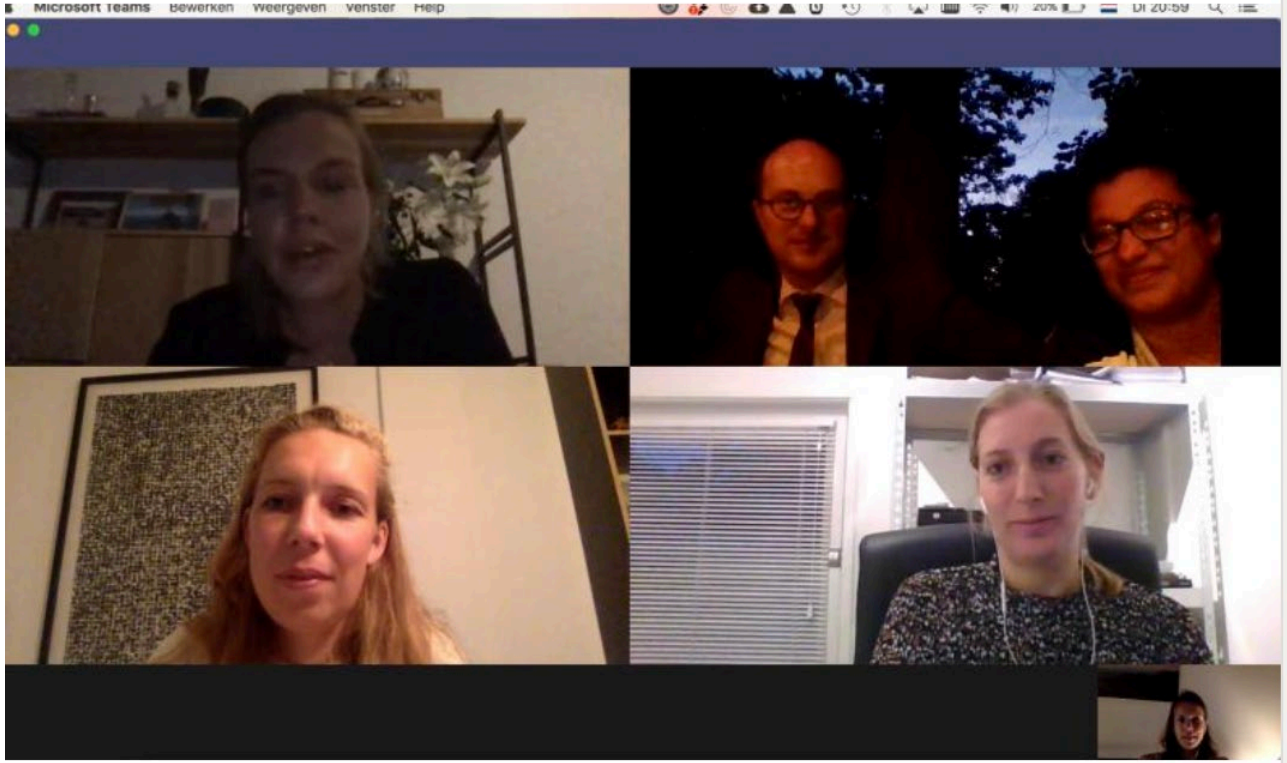
‘Straightforward’?

- **Dosering en spectrum antibioticum (toenemende resistentie Gram-negatieven)**
- **Exacte patiëntdefinitie (soort infectie, geboortetermijn)**
- **Aanpassing kinderformularium (nu geen orale AB < 1 maand oud)**
- **Aanpassing richtlijn**
- **Netwerkzorg; belangrijke rol voor 1e lijn in de 1e levensweken!**
- **Rol verzekeraars?**

Ouderparticipatieraad

Gerdien Tramper-Stranders
Pediatrician/clinical researcher & dean for research bij Franciscus Gasth...
1yr • Edited •

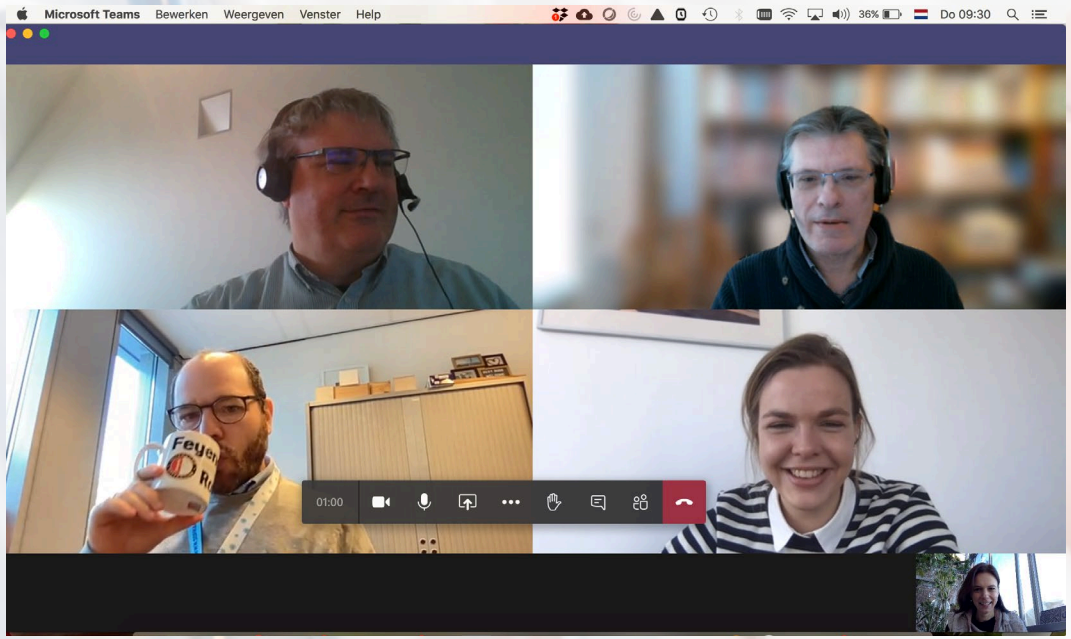
Patientparticipatie binnen de RAIN studie! Hier denken we met elkaar na over hoe we de onderzoeksresultaten straks gaan implementeren en welke rol patientvertegenwoordigers hierin hebben. **ZonMw Fleur Keij, MD Franciscus Gasthuis & Vlietland Erasmus MC**
www.rainstudie.nl



32 1 comment

Like Comment Share Send

DANK AAN IEDEREEN!



Ouders en deelnemers

Hoofdonderzoekers en lokale research teams

Ziekenhuisapotheek Erasmus MC

Data Safety Monitoring Board

Ondersteunende afdelingen

Ouderparticipatieraad

Erasmus MC Universitair Medisch Centrum Rotterdam

Innovatiefonds Zorgverzekeraars

European Society for Paediatric Research

SOPHIA Kinderziekenhuis Fonds

ESPID

ZonMw

franciscus Gasthuis & Vlietland

Hakon et al, Pediatrics 2021

Populatie studie 2015-2019
n = 282 046 neonaten
≥ 34 weken

2.6% van de populatie AB
2.9% positieve kweek

Clinical sepsis:
Klinische symptomen
CRP > 30 mg/L
≥5 dagen antibiotica

2019 aantal pt ab = 1218
Culture positive: 34 (2.8%)
Clinical: 325 (26.7%)
No sepsis: 859 (70.5%)

NNT: 36

TABLE 2 Duration of Antibiotic Treatment in Days and Numbers With a Diagnosis

	2015	2016	2017	2018	2019	$P^{a,b}$
Overall, mean (SD), d	3.9 (3.0)	3.9 (3.1)	3.5 (2.6)	3.6 (2.9)	3.4 (2.6)	<.001
Duration by region, mean (SD), d						
South-East	4.0 (2.9)	4.0 (3.1)	3.6 (2.6)	3.8 (3.0)	3.5 (2.3)	<.001
West	3.1 (2.4)	3.5 (3.3)	3.0 (2.3)	3.2 (2.8)	3.4 (3.5)	.54
Central	4.3 (3.6)	4.0 (3.2)	3.8 (3.1)	3.6 (2.8)	3.4 (2.6)	.09
North	4.3 (4.0)	3.3 (2.4)	3.3 (2.8)	3.1 (1.9)	3.2 (2.2)	.006
Duration by diagnosis, mean (SD), d						
Culture-positive sepsis	8.9 (5.9)	8.8 (5.5)	8.9 (5.2)	9.5 (5.8)	9.1 (5.0)	.98
Clinical sepsis	5.3 (2.9)	5.4 (2.9)	5.0 (2.6)	5.0 (2.5)	5.0 (2.3)	.01
No sepsis	2.9 (2.3)	2.8 (2.3)	2.6 (1.9)	2.8 (2.3)	2.7 (1.9)	.02
Numbers with diagnosis, *n* (%)						
Culture-positive sepsis	47 (0.08)	52 (0.09)	34 (0.06)	38 (0.07)	34 (0.06)	.34
Clinical sepsis	609 (1.0)	523 (0.9)	413 (0.7)	364 (0.7)	325 (0.6)	<.001
No sepsis	1159 (1.9)	1044 (1.7)	957 (1.7)	885 (1.6)	859 (1.6)	<.001

[a] One-way analysis of variance with logarithmic transformation for trend for duration during the period of 2015–2019.
[b] χ^2 test for change in numbers with diagnosis during the period of 2015–2019.

TABLE 3 Growth of Pathogens in Blood Cultures from Newborns in Norway During 2015–2019 (n = 213)

	2015	2016	2017	2018	2019	Total
GBS	15	20	14	13	11	73
Other streptococci	4	7	2	5	4	22
S aureus	7	8	5	6	5	31
E coli	9	10	9	7	7	42
Other specified bacteria[a]	11	8	5	5	7	36
Unspecified growth	2	2	0	2	3	9
Total (excluding CoNS,[b] fungi, and viruses)	48	55	35	38	37	213

If the culture had growth of 2 virulent organisms both were included (n = 2). Five children had 2 separate blood cultures with growth of different pathogens, thus the total number of infants with positive blood cultures is 206.
[a] Other specified bacteria (descending frequency): *Enterococcus*, other Gram-positive cocci, other Gram-positive rods, *Bacillus spp*, *Bacillus cereus*, *Enterobacter cloaca*, *Klebsiella oxytoca*, *Acinetobacter spp*, other Gram-negative cocci, and 1 anaerobe.
[b] A total of 133 blood cultures revealed growth of CoNS, and 83 of 133 (62%) received ≥5 d of antibiotics.

Stoll et al, Jama Pediatr 2020
Supplementary material

eTable 17. Mortality by Gestational Age and Birth Weight for Infants With Early Onset Infection

	n/N cases (%)		
	All	GBS	E coli
All deaths	38/235 (16)	4/70 (6)	27/85 (32)
By gestational age, weeks			
22-28	29/67 (43)	3/5 (60)	20/44 (45)
29-33	7/50 (14)	1/9 (11)	5/20 (25)
34-36	2/14 (14)	0/3 (0)	2/4 (50)
≥ 37	0/104 (0)	0/53 (0)	0/17 (0)
By birth weight, grams			
401-1000	23/50 (46)	2/3 (67)	16/34 (47)
1001-1500	7/38 (18)	1/7 (14)	5/17 (29)
1501-2500	6/39 (15)	1/7 (14)	4/14 (29)
≥ 2501	2/108 (2)	0/53 (0)	2/20 (10)

Data for one infant with both GBS and E coli were included in all patient data but excluded from GBS and E coli columns.
NICHD Neonatal Research Network Early-Onset Sepsis Surveillance Study II (2015-2017)

eTable 3. *Escherichia coli* Early-Onset Sepsis Rates per 1000 Live Births (LBs) by Study Center and Gestational Age

Center	Rate/1000 LBs (95% CI), n/N[1]				
	All	GA 22-28 w	GA 29-33 w	GA 34-36 w	GA 37+ w
A	0.64 (0.21-1.49)	17.24 (3.57-49.56)	2.76 (0.07-15.29)	1.19 (0.03-6.61)	0 (0-0.57)
	5/7853	3/174	1/362	1/840	0/6474
B	0.42 (0.20-0.78)	16.30 (3.38-46.91)	1.90 (0.05-10.57)	0 (0-2.14)	0.28 (0.10-0.61)
	10/23664	3/184	1/525	0/1721	6/21234
C	0.69 (0.14-2.02)	43.48 (9.06-121.8)	0 (0-29.78)	0 (0-10.57)	0 (0-1.11)
	3/4347	3/69	0/122	0/347	0/3330
D	0.34 (0.11-0.79)	12.15 (2.51-35.08)	2.42 (0.06-13.38)	0.85 (0.02-4.72)	0 (0-0.28)
	5/14848	3/247	1/414	1/1177	0/13010
E	0.33 (0.11-0.78)	8.29 (1.71-24.03)	1.56 (0.04-8.69)	0 (0-3.04)	0.08 (0.00-0.43)
	5/15050	3/362	1/639	0/1210	1/12839
F	0.63 (0.08-2.26)	0 (0-64.87)	13.70 (1.66-48.61)	0 (0-12.14)	0 (0-1.37)
	2/3189	0/55	2/146	0/302	0/2686
G	0.17 (0.03-0.49)	5.46 (0.14-30.07)	4.25 (0.51-15.25)	0 (0-2.86)	0 (0-0.23)
	3/17849	1/183	2/471	0/1290	0/15905
H	0.34 (0.07-0.98)	26.32 (5.46-74.98)	0 (0-14.25)	0 (0-5.05)	0 (0-0.47)
	3/8939	3/114	0/257	0/729	0/7841
I	0.59 (0.19-1.37)	11.05 (3.02-28.05)	0 (0-6.05)	1.06 (0.03-5.89)	0 (0-0.56)
	5/8488	4/362	0/608	1/943	0/6575
J	1.08 (0.56-1.89)	23.18 (9.37-47.17)	3.15 (0.38-11.35)	0.66 (0.02-3.65)	0.23 (0.03-0.84)
	12/11066	7/302	2/634	1/1524	2/8606
K	0.22 (0.08-0.49)	8.23 (2.25-20.94)	0 (0-4.16)	0 (0-1.61)	0.09 (0.01-0.32)
	6/26730	4/486	0/885	0/2294	2/22929
L	0.22 (0.05-0.65)	0 (0-15.00)	1.68 (0.04-9.31)	0 (0-2.79)	0.18 (0.02-0.64)
	3/13482	0/244	1/596	0/1321	2/11319
M	0.41 (0.16-0.84)	25.00 (6.85-62.77)	3.70 (0.45-13.31)	0 (0-2.39)	0.07 (0.00-0.37)
	7/17143	4/160	2/540	0/1539	1/14904
N	0.55 (0.11-1.61)	16.39 (0.41-87.99)	4.27 (0.11-23.58)	0 (0-6.65)	0.22 (0.01-1.21)
	3/5456	1/61	1/234	0/553	1/4608
O	0.28 (0.09-0.65)	10.87 (1.32-38.71)	2.26 (0.06-12.54)	0 (0-2.79)	0.13 (0.02-0.45)
	5/17886	2/184	1/442	0/1318	2/15944
P	0.35 (0.10-0.90)	7.41 (0.90-26.50)	2.94 (0.36-10.58)	0 (0-3.56)	0 (0-0.39)
	4/11385	2/270	2/680	0/1035	0/9401
Q	0 (0-22.79)	0 (0-308.5)	0 (0-102.8)	0 (0-67.23)	0 (0-56.87)
	0/160	0/10	0/34	0/53	0/63
R	0.50 (0.16-1.17)	6.21 (0.16-34.12)	6.42 (1.33-18.66)	0 (0-3.69)	0.12 (0.00-0.67)
	5/9945	1/161	3/467	0/999	1/8302

[1]Clopper-Pearson confidence intervals (CI) are shown. NICHD Neonatal Research Network Early-Onset Sepsis Surveillance Study II (2015-2017)