Oral Antibiotics in Neonates: Time to Switch?

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Acknowledgements and Disclosures

Thank you to the organisers for the invitation

I will discuss the neonatal use of antibiotics that may not be approved by national guidelines or formularies

I have received financial support from the following companies, but will not be discussing their products:

- Chiesi – Curosurf surfactant
- Inspiration Healthcare plc – Medical Technologies
- Vapotherm – Precision Flow & OAM
- Biofloratech Ltd – Labinic probiotic

Closing the loop…

Vision

"We will be a leading neonatal unit for non-invasive care, focused on achieving the best clinical outcomes in the country"

Crazy Goal

"To have the lowest BPD rates in the country"

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Welcome to NNAP Online, the interactive reporting tool for the National Neonatal Audit Programme

The National Neonatal Audit Programme (NNAP) is a national clinical audit run by the Royal College of Paediatrics and Child Health (RCPCH) on behalf of the NHS. It is commissioned by the Healthcare Quality Improvement Partnership (HQIP).

The NNAP aims to helps neonatal units improve care for babies and their families by identifying areas for quality improvement in relation to the delivery and outcomes of care.

NNAP Online is a reporting tool which provides access to audit results.

You can use NNAP Online to:

- view an overall annual summary report for a chosen neonatal unit or network for 2014 to 2022 NNAP results
- view and compare the results for specific NNAP audit measures for different units, unit designations or networks
- view, via the outlier analysis section, whether a 2022 result for a unit or network is outside the expected range
- download a unit-specific poster of NNAP results for display in your unit

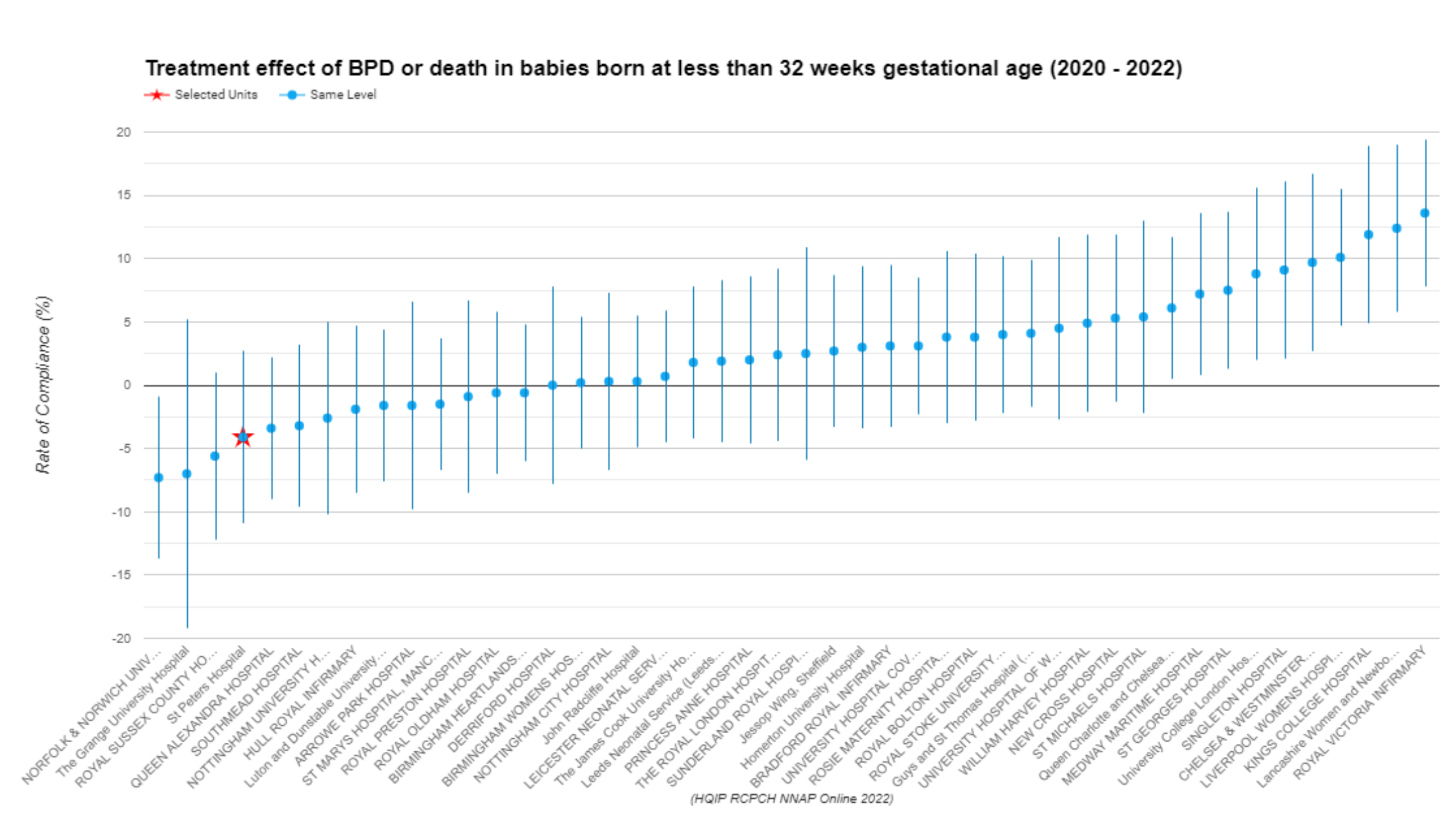
Links to other resources on 2022 data, including the summary report, guide for parents and carers, and summary infographic poster are available at: www.rcpch.ac.uk/nnap-report-2022-data

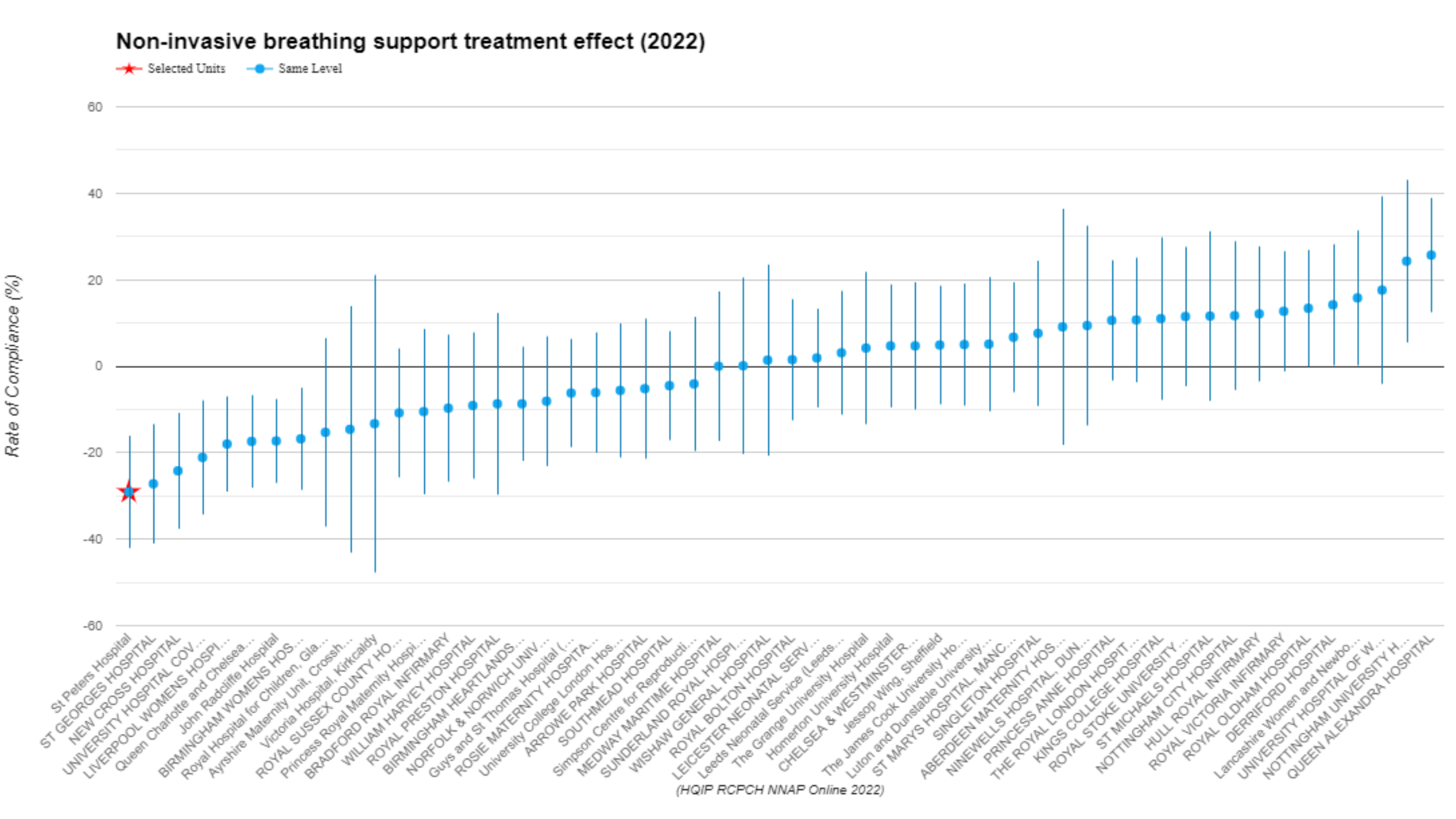
If you have any questions about the NNAP, or this reporting tool, then please contact the NNAP project team at: nnap@rcpch.ac.uk

For further information and to access the full range of NNAP resources, please visit: www.rcpch.ac.uk/nnap

New NNAP frequent reporting data dashboard

Detailed audit results are now also available via the new NNAP data dashboard. The dashboard presents results for each of the 10 NNAP performance metrics introduced in 2023 as annual rolling averages, updated quarterly. Results can be displayed for neonatal units, Integrated Care Systems and Health Boards (Wales and Scotland), and by neonatal network and can be found here: www.rcpch.ac.uk/NNAP-data-dashboard


Treatment effect of BPD or death in babies born at less than 32 weeks gestational age (2020 - 2022)
Selected Units
Same Level
Rate of Compliance (%)
20
15
10
5
0
-5
-10
-15
-20
NORFOLK & NORWICH UNIV…
The Grange University Hospital
ROYAL SUSSEX COUNTY HO…
St Peters Hospital
QUEEN ALEXANDRA HOSPITAL
SOUTHMEAD HOSPITAL
NOTTINGHAM UNIVERSITY H…
HULL ROYAL INFIRMARY
Luton and Dunstable University…
ARROWE PARK HOSPITAL
ST MARYS HOSPITAL, MANC…
ROYAL PRESTON HOSPITAL
ROYAL OLDHAM HOSPITAL
BIRMINGHAM HEARTLANDS…
DERRIFORD HOSPITAL
BIRMINGHAM WOMENS HOS…
NOTTINGHAM CITY HOSPITAL
John Radcliffe Hospital
LEICESTER NEONATAL SERV…
The James Cook University Ho…
Leeds Neonatal Service (Leeds…
PRINCESS ANNE HOSPITAL
THE ROYAL LONDON HOSPIT…
SUNDERLAND ROYAL HOSPI…
Jessop Wing, Sheffield
Homerton University Hospital
BRADFORD ROYAL INFIRMARY
UNIVERSITY HOSPITAL COV…
ROSIE MATERNITY HOSPITA…
ROYAL BOLTON HOSPITAL
ROYAL STOKE UNIVERSITY…
Guys and St Thomas Hospital (…
UNIVERSITY HOSPITAL OF W…
WILLIAM HARVEY HOSPITAL
NEW CROSS HOSPITAL
ST MICHAELS HOSPITAL
Queen Charlotte and Chelsea…
MEDWAY MARITIME HOSPITAL
ST GEORGES HOSPITAL
University College London Hos…
SINGLETON HOSPITAL
CHELSEA & WESTMINSTER…
LIVERPOOL WOMENS HOSPI…
KINGS COLLEGE HOSPITAL
Lancashire Women and Newbo…
ROYAL VICTORIA INFIRMARY
(HQIP RCPCH NNAP Online 2022)


Non-invasive breathing support treatment effect (2022)
Selected Units
Same Level
60
40
20
0
-20
-40
-60
Rate of Compliance (%)
St Peters Hospital
ST GEORGES HOSPITAL
NEW CROSS HOSPITAL
UNIVERSITY HOSPITAL COV...
LIVERPOOL WOMENS HOSPI...
Queen Charlotte and Chelsea...
John Radcliffe Hospital
BIRMINGHAM WOMENS HOS...
Royal Hospital for Children, Gla...
Ayrshire Maternity Unit, Crossh...
Victoria Hospital, Kirkcaldy
ROYAL SUSSEX COUNTY HO...
Princess Royal Maternity Hospi...
BRADFORD ROYAL INFIRMARY
WILLIAM HARVEY HOSPITAL
ROYAL PRESTON HOSPITAL
BIRMINGHAM HEARTLANDS...
NORFOLK & NORWICH UNIV...
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SOUTHMEAD HOSPITAL
MEDWAY MARITIME HOSPITAL
SUNDERLAND ROYAL HOSPI...
WISHAW GENERAL HOSPITAL
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ABERDEEN MATERNITY HOS...
SINGLETON HOSPITAL
NINEWELLS HOSPITAL, DUN...
PRINCESS ANNE HOSPITAL
THE ROYAL LONDON HOSPIT...
KINGS COLLEGE HOSPITAL
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NOTTINGHAM UNIVERSITY H...
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(HQIP RCPCH NNAP Online 2022)

Aims

- Background – Neonatal Early Onset Sepsis
- Evidence for Oral Antibiotics
- Changing practice

Early Onset Sepsis (EOS)

- Bacterial infection ≤72 h of birth
- Incidence of ~1/1000 live births
- More common in premature and/or VLBW infants
- 45% childhood deaths <5 yrs occurs in the neonatal period, of which 22% is due to neonatal infection

National Guidance (NICE 2021) Neonatal infection: antibiotics for prevention and treatment

https://www.nice.org.uk/guidance/ng195

Diagnosis & Treatment - challenges

- Non-specific symptoms
- Delayed and non-specific inflammatory markers
- Clinical ‘fear’ of missing something treatable
- A prolonged IV course interferes with family bonding to baby, is expensive and may require several IV line attempts

- Adoption of "Kaiser Permanente" risk calculator has resulted in >50% fewer babies >35 weeks receiving antibiotics in our unit

https://neonatalsepsiscalculator.kaiserpermanente.org/

Neonatal Early-Onset Sepsis Calculator

Please enter details below.

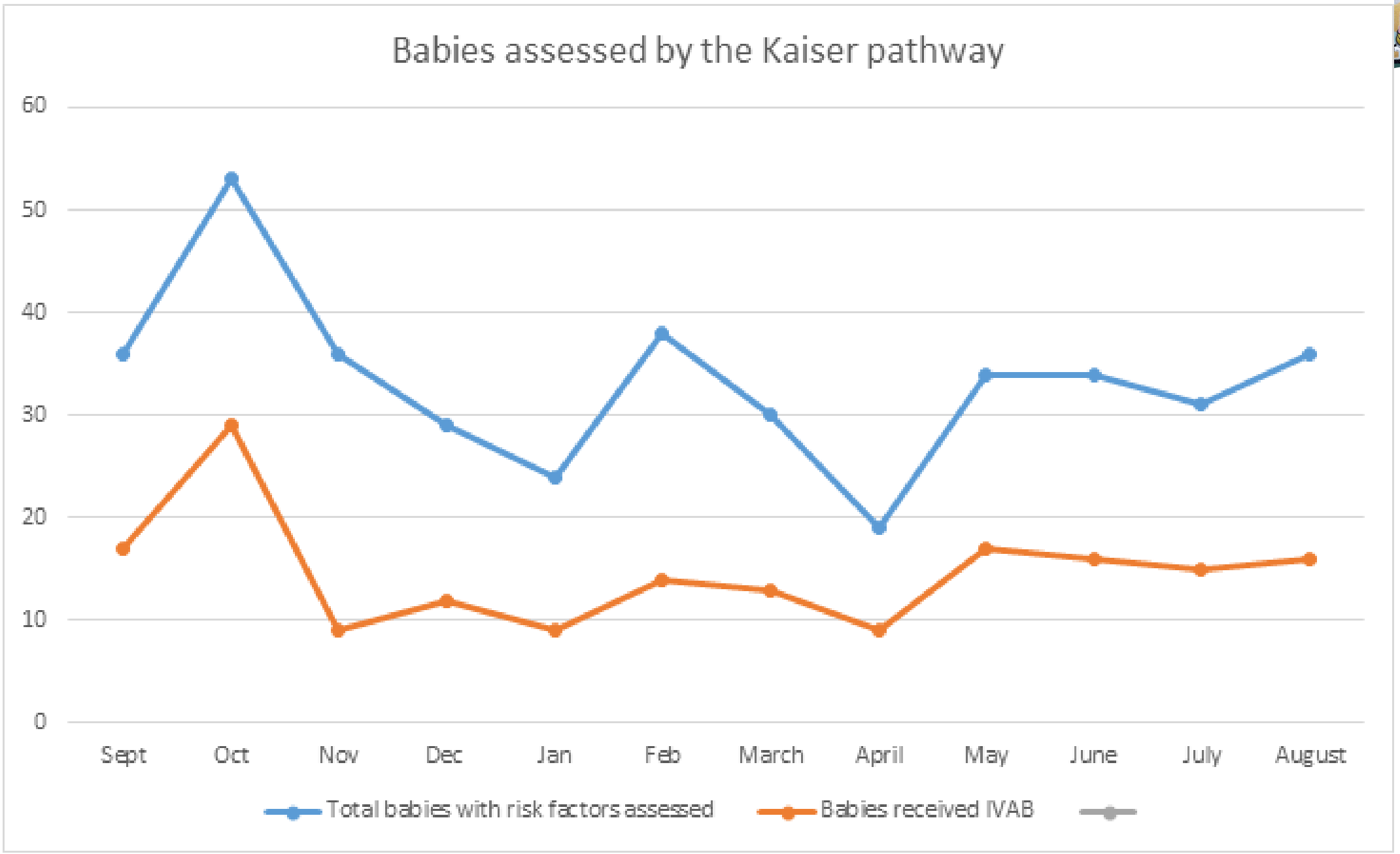
Predictor	Scenario
Incidence of Early-Onset Sepsis	0.5/1000 live births (CDC nationa
Gestational age	40 weeks; 0 days
Highest maternal antepartum temperature	38 Celsius
ROM (Hours)	12
Maternal GBS status	○ Negative ○ Positive ◉ Unknown
Type of intrapartum antibiotics	◉ Broad spectrum antibiotics > 4 hrs prior to birth ○ Broad spectrum antibiotics 2-3.9 hrs prior to birth ○ GBS specific antibiotics > 2 hrs prior to birth ○ No antibiotics or any antibiotics < 2 hrs prior to birth

Calculate » Clear

Risk per 1000/births	
EOS Risk @ Birth	0.23

EOS Risk after Clinical Exam	Risk per 1000/births	Clinical Recommendation	Vitals
Well Appearing	0.09	No culture, no antibiotics	Routine Vitals
Equivocal	1.13	Blood culture	Vitals every 4 hours for 24 hours
Clinical Illness	4.77	Empiric antibiotics	Vitals per NICU

Classification of Infant's Clinical Presentation Clinical Illness Equivocal Well Appearing


Babies assessed by the Kaiser pathway
60
50
40
30
20
10
0
Sept
Oct
Nov
Dec
Jan
Feb
March
April
May
June
July
August
Total babies with risk factors assessed
Babies received IVAB

Oral Switch is routine practice in older patients

- Oral switch therapy, once the patient is clinically well, is safe and effective in Paediatrics and Adult medicine

- What's the evidence to change neonatal practice?

What do we know?

- C_{max} varies in both IV and oral
- T_{max} is slower for IV vs oral
- Efficacy for oral antibiotics depends on $T_{>MIC}$
- MIC is pathogen and antibiotic specific

Systematic Review 2019

- Evidence for oral antibiotic and achievement of serum concentrations in neonates
- 31 studies met inclusion criteria
  - 4 studies – healthy newborns
  - 2 studies – oral switch
  - 13 studies in LMICs
- Absorption – T_{max} 2-4 hrs
- Efficacy – (Amoxycillin)
  - $T_{>MIC}$ exceeded for E. coli and GBS at 25-50 mg/kg/dose 6 hourly
  - No excess of relapse

Mir F et al. Arch Dis Child. 2020;105(12):1208-1214
Gras-Le Guen C *et al.* Eur J Clin Pharmacol. 2007;63(7):657-62
Fleur M Keij *et al.* Journal of Antimicrobial Chemotherapy. 2019: 74, (11);150–3161

Efficacy and safety of switching from intravenous to oral antibiotics (amoxicillin–clavulanic acid) versus a full course of intravenous antibiotics in neonates with probable bacterial infection (RAIN): a multicentre, randomised, open-label, non-inferiority trial

Fleur M Keij, René F Kornelisse, Nico G Hartwig, Jacqueline van der Sluijs-Bens, Ron H T van Beek, Arianne van Driel, Linda G M van Rooij, Ilka van Dalen-Vink, Gertjan J A Driessen, Sandra Kenter, Jeannette S von Lindern, Marianne Eijkemans, Gerda M Stam-Stigter, Hongchao Qi, Maartje M van den Berg, Martin G A Baartmans, Laura H van der Meer-Kappelle, Clemens B Meijssen, Obbe F Norbruis, Jojanneke Heidema, Maaike C van Rossem, Paul C P den Butter, Karel Allegaert, Irwin K M Reiss, Gerdien A Tramper-Stranders

Reduction of intravenous **A**ntibiotics **I**n **N**eonates

Keij FM, *et al*. Lancet Child Adolesc Health. 2022;6(11):799-809

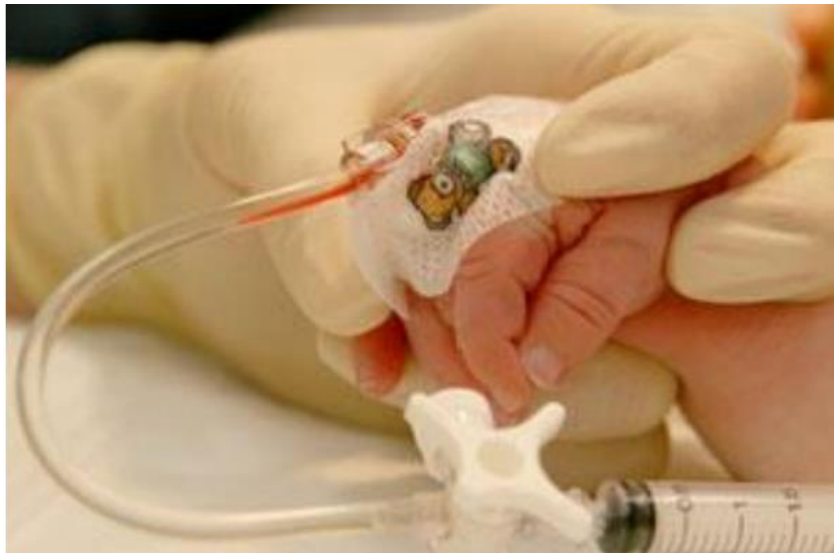
RAIN Study - enrolment

- 19 sites in Netherlands
- >35 weeks
- >2kg
- Planned for 7-day antibiotic course for probable bacterial infection

Exclusions included:

- Infection ruled out (antibiotics ceased)
- Infection ruled in (culture-proven or severe clinical sepsis)

"Probable" bacterial infection



- Maternal risk factors
- Clinical symptoms but improved
- Elevated inflammatory parameters
- Negative blood culture
- Tolerating oral feeding

- Plan to continue antibiotic course beyond 36 - 48hr duration

Primary study outcome

Bacterial reinfection within 28 days of treatment completion

Defined as

- Clinical symptoms
- Infection and fever (>38·0°C)
- Hypothermia (<36·0°C)
- Elevated CRP (≥10 mg/L) or PCT (≥0·5 ng/mL)

Secondary outcomes included infection, quality markers, PK studies, microbiome analysis

Study Protocol

- Randomised to
  - Continue intravenous (Pen & Gent) and remain in hospital
  - Switch to oral (Augmentin) and home once tolerating
- Both groups received 7 days in total antibiotics

Results

- 829 assessed, 510 enrolled, 253 received intervention
- Median GA 40·3 weeks

	Oral amoxicillin–clavulanic acid (n=252)	Intravenous antibiotics (n=252)
Group B *Streptococcus* status		
Previous child with Group B *Streptococcus* infection	1 (<1%)	1 (<1%)
Colonised	25 (10%)	24 (10%)
Not colonised	54 (21%)	42 (17%)
Not screened	172 (68%)	185 (73%)
Prolonged rupture of membranes (>24 h)†	85/247 (34%)	75/249 (30%)
Maternal fever (>38·0°C)	121 (48%)	109 (43%)
Suspected intra-uterine infection requiring antibiotic treatment	79 (31%)	65 (26%)
Clinical symptoms at onset of infection‡	201 (80%)	219 (87%)
Respiratory	166 (83%)	173 (79%)
Circulatory	49 (24%)	60 (27%)
Gastrointestinal	28 (14%)	27 (12%)
Neurological	25 (12%)	42 (19%)
Temperature instability (<36·5°C or >38·0°C)	82 (41%)	73 (33%)
Behavioural changes	51 (20%)	33 (13%)
Requiring any respiratory support	95 (38%)	101 (40%)
C-reactive protein, mg/L		
T0 h	4·0 (1·0–19·0)	5·8 (1·4–20·3)
T24 h	29·0 (19·0–53·3)	32·0 (19·0–49·5)
Elevated C-reactive protein concentrations (≥10 mg/L)		
T0 h§	104 (42%)	112 (45%)
T24 h¶	223 (95%)	220 (96%)
Procalcitonin, ng/mL‖		
T0 h	5·6 (1·6–19·0)	7·0 (3·6–14·1)
T24 h	13·4 (4·8–32·0)	12 (6·0–21·4)
Elevated procalcitonin concentrations**		
T0 h (≥0·25 ng/mL)	64 (97%)	63 (98%)
T24 h (≥10 ng/mL)	39 (57%)	36 (58%)
Cerebrospinal fluid culture	17 (7%)	18 (7%)
Urine culture	7 (3%)	4 (2%)

Results

- Oral switch after 7 tds IV doses well tolerated
- Compliance with antibiotic plan 98% oral, 80% IV
- 49 patients in IV group could not complete due to IV access difficulties and were either switched to oral (67%), IM (6%) or discontinued (27%)

  =>Protocol violation ($p<0.0001$)
- 1 baby per group readmitted for probable bacterial infection (<1%)
- Hospitalisation 3.4 vs 6.8 days (50% reduction - $p<0.0001$)

- No increase in adverse events

Comments

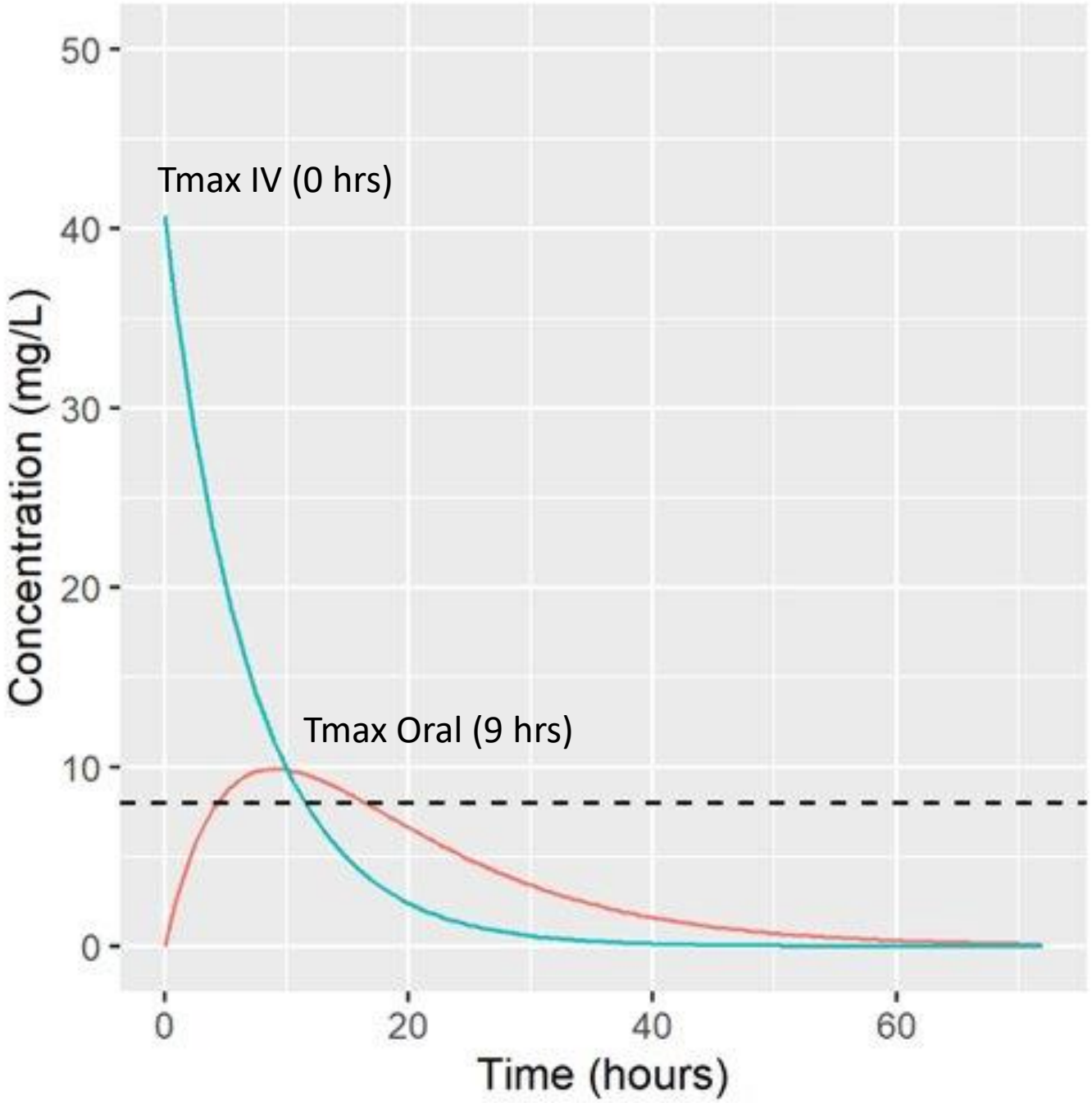
Similar protocols to UK

CRP increased at 24hrs to 19-53 mg/L in oral antibiotic group

High rates of respiratory symptoms 83% in oral and 79% in IV

39% needed respiratory support – included in RAIN Study

20% of oral and 13% of IV groups no clinical symptoms – would they have been "no culture, no ab's" in Kaiser Permanente guidelines?



Concentration time profile after single oral and intravenous dose of 25 mg/kg (75 mg/kg/day)

Tmax for oral dose reached after 9 hours.

$T_{>MIC}$ 6hrs

Tmax IV reached immediately

$T_{>MIC}$ 12hrs

Keij FM et al Clin Infect Dis. 2023; 30;77(11):1595-1603

Oral switch - Sweden

Two era retrospective study guided by clinical signs and CRP

Single centre. Term ≥37+0.

- 2016 - 2017 n=140 (7 days of IV) - Culture positive n=7
- 2018 - 2019 n=97 (5 days of antibiotics (3 IV, 2 oral)) - Culture positive n=5

Culture negative EOS defined as

- Clinical signs (e.g. respiratory, cardiovascular, GI, irritability, lethargy)
- CRP >20mg/L (maximum 80mg/L, decreasing by at least 50% during first 72 hrs

Gyllensvärd, J *et al* BMC Pediatr **20**, 531 (2020)

Outcomes

- No reinfection or mortality
- Rate of culture positive EOS was 1/1000 live births
- Reduction in hospital stay from 7 to 5 days
- This equated to annual bed-day saving of Euro 122,000

Gyllensvärd, J *et al* BMC Pediatr **20**, 531 (2020)

Oral Switch - Denmark

- Prospective cohort study
- 489 term neonates switched to oral antibiotics after 48 hrs
- Eligible if stable, tolerating feeds, no clinical meningitis
- 7-14 day course

- No readmissions
- 11 babies with positive blood cultures also switched to oral

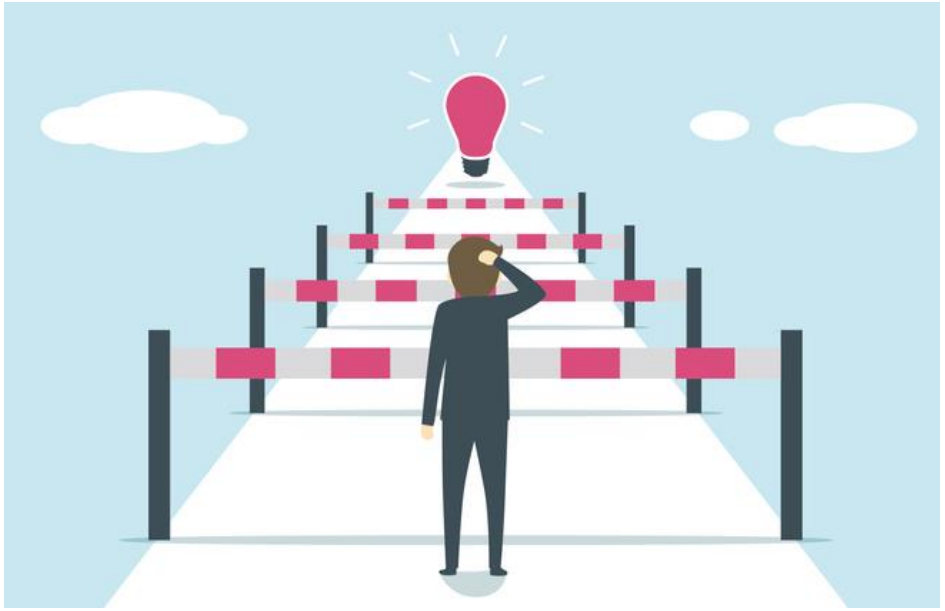
Implementing an Oral Switch QI

Reasons?

- Because we are (sometimes) already doing it
- Baby & family friendly
- Evidence of safety and effectiveness
- Antibiotic stewardship

What are the potential barriers?

- Some units may already have a protocol for oral use of antibiotics
- Concerns about additional risks
- Off-label use of oral antibiotic in age-group
- Not within NICE(UK) guidelines



Kent, Surrey, Sussex – Neonatal Network Data

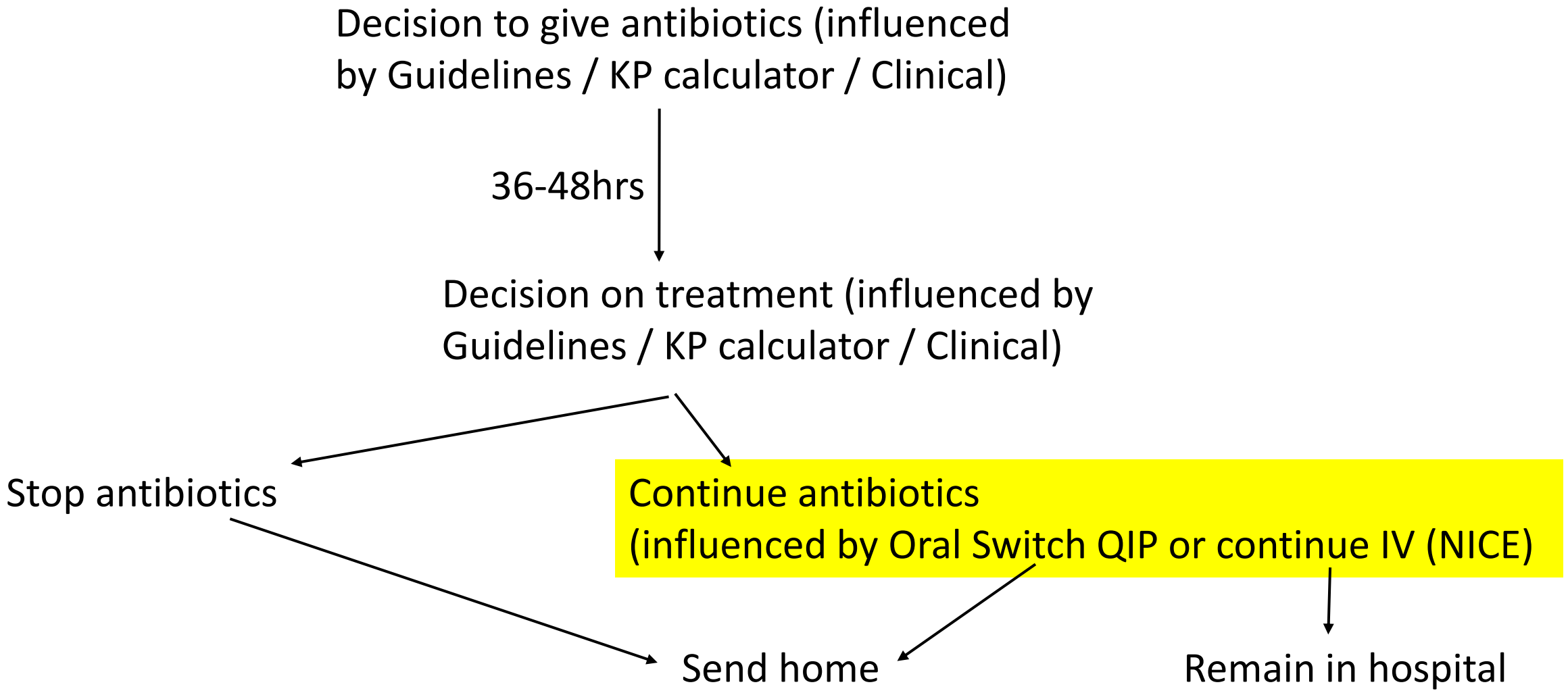
Babies born in 2022 admitted to TC who had antibiotics for 5+ days by 'principle reason for admission'

	Hypoglycaemia	Infection	Jaundice	NK	Other	Resp	Grand Total
Darent Valley		36	3		1	4	44
East Surrey	1	4					5
East Sussex		28					28
Frimley Park		34	2		1		37
Medway Maritime		12			3	1	16
PRH, Haywards Heath	2	30			3		35
QEQM, Margate		19					19
Royal Surrey County		4		1	1		6
Royal Sussex County		20		2			22
St Peter's, Chertsey		11	1		1		13
Tunbridge Wells		83					83
William Harvey, Ashford		40	1			1	42
Worthing		30	2				32
Grand Total	**3**	**351**	**9**	**3**	**10**	**6**	**382**

Scale of the issue

- 382 babies had antibiotics for 5+ days
- RAIN data (3.4 vs 6.8 days) would mean up to 1299 inpatient days saved
- Does not include admissions to neonatal unit for resp / other support
- What are the gains?
  - **Baby** – less cannulation attempts, home earlier
  - **Parents** – family friendly, bonding, less invasive procedures
  - **Hospital** – reduction in bed days, cost reductions
  - **System** – across network, significant gains and savings could be realised

Where does an "oral switch" QIP fit?



Which babies might we include?

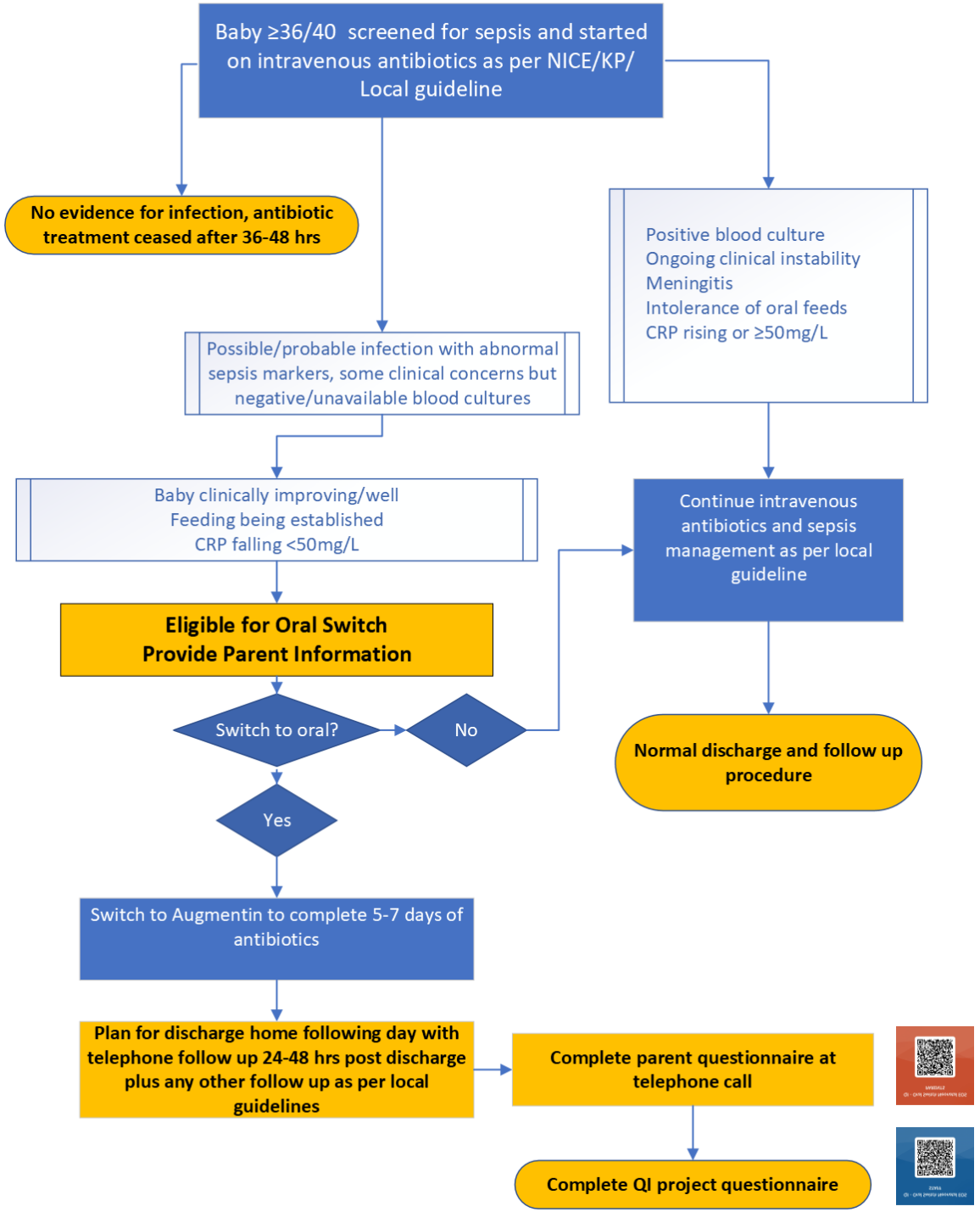
Babies who are well but have some persistent but improving abnormalities (e.g. falling CRP, respiratory symptoms) in whom a course of antibiotics is recommended (local decision)

- Avoid unnecessary antibiotics
- Avoid "threshold creep" by defining eligibility carefully
- Monitor data (Quality Improvement project)
- Recognise caution is needed initially

Oral Antibiotic - Details

- First oral dose given between 3 and 6 hrs after the last IV dose to allow for continuous effective serum concentrations
- Oral doses given 10-20 minutes before a feed
- Parents
  - Information leaflet
  - Shown how to prepare & administer
  - Phone call after discharge includes questionnaire
- Co-amoxiclav 125/31 SF oral suspension 25 mg/kg 8 hrly

Protocol


Baby ≥36/40 screened for sepsis and started on intravenous antibiotics as per NICE/KP/ Local guideline
No evidence for infection, antibiotic treatment ceased after 36-48 hrs
Positive blood culture
Ongoing clinical instability
Meningitis
Intolerance of oral feeds
CRP rising or ≥50mg/L
Possible/probable infection with abnormal sepsis markers, some clinical concerns but negative/unavailable blood cultures
Baby clinically improving/well
Feeding being established
CRP falling <50mg/L
Continue intravenous antibiotics and sepsis management as per local guideline
Eligible for Oral Switch
Provide Parent Information
Switch to oral?
No
Yes
Normal discharge and follow up procedure
Switch to Augmentin to complete 5-7 days of antibiotics
Plan for discharge home following day with telephone follow up 24-48 hrs post discharge plus any other follow up as per local guidelines
Complete parent questionnaire at telephone call
Complete QI project questionnaire

Unknown effects of oral switch

- Breastfeeding rates
- Community antibiotic resistance
- Gut microbiome (dysbiosis)

Clinical Scenario

- Term baby
- Known PROM 24 hrs, unknown maternal GBS status
- Presents with tachypnoea at 1 hr of postnatal age
- Infection screen (FBC, CRP, BC) and IV antibiotics started
- First CRP 45 mg/L. No LP performed as no meningism
- At 48 hrs tachypnoea settled, feeding well, not irritable, examines normally, BC negative, CRP 21mg/L
- Consultant decision for 5 days of antibiotics

Question?

Who would (now) consider switching to oral antibiotics and send baby home?

Summary

- There is good scientific and clinical evidence to support the Oral Switch of antibiotics in neonates

- What's our Crazy Goal?

"To have the Oral Switch Guideline implemented in every Hospital in our Neonatal Network, covering 48,000 births, by the end of this year"

Thank you again, until next time we meet

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