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A simulation study of antimicrobial resistance carriage in neonatal intensive care units: implications for cluster-randomised trials

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Highlights

- For a parallel cluster-randomised trial evaluating the impact of an IPC intervention on prevalence of AMR genes carriage a very high number of sites or restriction to high prevalence settings is required
- The sampling frequency has only minimal impact on the power of such a trial

Introduction

- Premature neonates in the neonatal intensive care unit (NICU) frequently experience hospital-acquired infections
- Infection prevention and control (IPC) interventions aim to reduce carriage with antimicrobial resistant (AMR) bacteria in infants in the NICU
- We explored the power of a parallel cluster-randomised trial evaluating the impact of an IPC intervention on prevalence of AMR genes carriage in very premature neonates in the NICU

Methods

Data collection:

- 24 NICUs / 8 countries in the NeoIPC feasibility study[1]
- Neonates born <32 weeks gestational age
- Four point-prevalence surveys (PPSs) every 4, 7, or 10 days
- PCR on stool for ESBL, CPE, and VRE genes
  CTX-M group 1 and 9, blaIMP, blaKPC, blaNDM, blaOXA-48, blaVIM, vanA, vanB

Statistics

- Step 1: Mixed effects logistic regression to determine relation between admission duration and prevalence of AMR genes, accounting for infant and NICU level clustering
- Step 2: Simulation of a parallel cluster-randomised trial based on the modeled cluster and time effects, assuming
  - Trial duration 12 months
  - 25% missing stool samples
  - 32 to 256 NICUs
  - Weekly to monthly stool samples
  - Length of NICU stay based on published data[2]
  - Odds ratio for intervention effect between 0.8 and 0.5
- Main outcome: power of each set of design characteristics to detect a reduction in AMR genes carriage

Table 1: Study characteristics of very premature neonates

Country (# sites)	Neonates (N)	# samples (N)	Any AMR genes detected: N (%)
Switzerland (4)	49	109	2 (1.8)
Germany (1)	16	37	4 (10.8)
Estonia (2)	7	20	0 (0.0)
Greece (6)	47	115	53 (46.1)
Italy (2)	15	28	7 (25.0)
Poland (1)	10	18	1 (5.6)
Spain (4)	51	143	42 (29.4)
United Kingdom (4)	82	163	10 (6.1)

Abbreviations: AMR: antimicrobial resistance

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Results

- Of 947 infant-PPS combinations, 631 (67%) provided stool samples, with AMR genes in 119/631 (19%) (Table 1)
- The best fitting model had a fixed effect for admission duration and random intercepts for NICU and infant (Table 2)
- Adequate power could only be attained with a very high number of NICUs or when restricting to NICUs from high-prevalence countries (Figure)
- The power was only minimally affected by the sampling frequency (Figure)

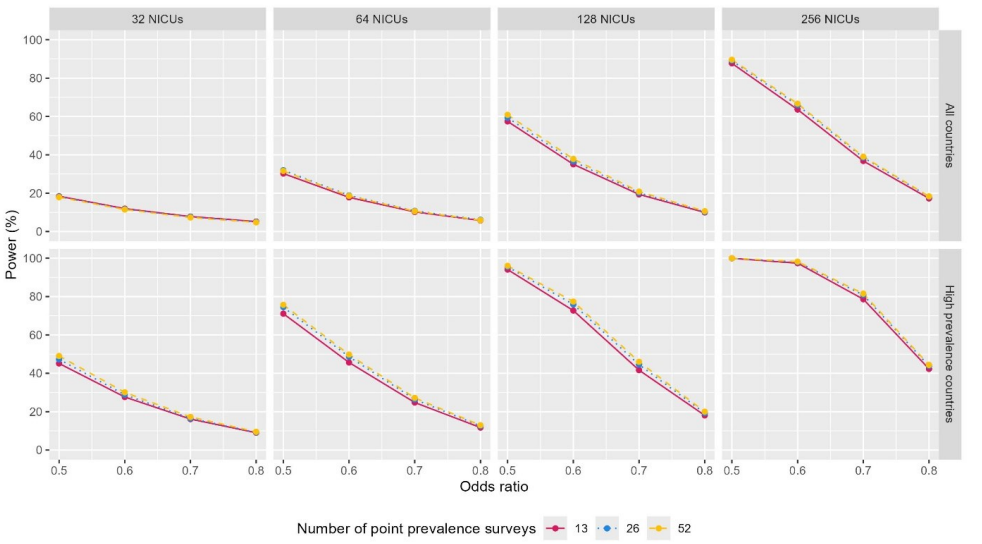
Table 2: Model parameters from the NeoIPC feasibility study

Parameter	Estimate	Standard error	OR (95% CI)
All feasibility sites			
Intercept	-3.824[1]	0.884	-
Admission duration (weeks)	0.105[1]	0.054	1.11 (1.00-1.24)
Infant	2.281[2]		-
Cluster	2.302[2]		-
High-prevalence sites[3]			
Intercept	-1.657[1]	0.651	
Admission duration (weeks)	0.152[1]	0.069	1.16 (1.03-1.37)
Infant (random intercept)	1.886[2]		
Cluster (random intercept)	1.243[2]		

[1] beta-coefficient. [2] standard error of the random intercept. [3] high-prevalence sites are those from Greece, Italy, and Spain. Abbreviations: OR: odds ratio, CI: confidence interval.

Figure: Power to detect reduced AMR genes carriage

Per set of design characteristics, 200 simulations were done. Sampling frequency: the number of point prevalence surveys in a 12-month trial period. For the scenario with high-prevalence countries, data from Greece, Italy, and Spain were used.



Conclusion:

To evaluate the impact of IPC interventions on prevalence of AMR genes carriage in a cluster-randomised trial in the NICU, a very large number of clusters or restriction to high-prevalence settings is required. Frequent sampling is not needed.

References:

[1] NeoIPC feasibility phase: Colonisation Surveillance. NeoIPC project website: https://neoipc.org/feasibility/

[2] S.E. Seaton et al. Estimating neonatal length of stay for babies born very preterm. Arch Dis Child Fetal Neonatal Ed. 2019 Mar;104(2):F182-F186. doi: 10.1136/archdischild-2017-314405.

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Learn more about the NeoIPC Project here!