How Many Newborns Must Be Treated To Find One Infection? A Simulation of Categorical and Multivariable Risk Stratification for Early-Onset Sepsis

Dr. Ayesha Sara

PharmD (Doctor of Pharmacy), Clinical Pharmacist, KIMS Hospital, Secunderabad, India.

Corresponding author: ayeshasara28@gmail.com

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Abstract

Background: Early-onset neonatal sepsis is rare and serious, so empirical antibiotics are given to many infants to treat few. Two approaches are in routine use: a categorical rule triggered by maternal risk factors, and a multivariable estimate combined with clinical examination. We quantified the antibiotic exposure each generates per case identified, and what the threshold choice determines.

Methods: We simulated 200,000 births with maternal risk factors, gestational age and clinical appearance, calibrated to a true infection prevalence of 0.86 per 1000. Both strategies treated any clinically ill infant regardless of score. Outcomes were the proportion receiving antibiotics, cases identified at birth, sensitivity, and the number of infants treated per case identified. The treatment threshold was varied from 0.5 to 10 per 1000 and true prevalence from 0.3 to 3.0 per 1000.

Results: The categorical rule gave antibiotics to 21.23% of infants, identified 125 of 172 cases (sensitivity 0.727) and treated 340 infants per case. The multivariable approach gave antibiotics to 4.45%, identified 121 cases (sensitivity 0.703) and treated 74 per case — a 4.6-fold difference in exposure for a difference of 4 cases. Varying the threshold from 0.5 to 10 per 1000 moved treatment from 59.2% to 0.65% of infants and sensitivity from 0.953 to 0.564. Across a tenfold range of true prevalence the categorical rule treated a near-constant share of infants, from 21.2% to 21.3%, while the multivariable approach scaled from 0.78% to 38.7%. No clinically ill infected infant went untreated under either strategy.

Conclusion: A categorical rule cannot respond to how much infection a population has. The threshold in a multivariable approach is a value judgement about acceptable exposure, not a statistical quantity, and clinical examination rather than any score was what protected the ill infants.

Keywords: Early-Onset Neonatal Sepsis, Antibiotic Stewardship, Risk Stratification, Clinical Decision Rules, Neonatal Intensive Care, Number Needed To Treat.

1. INTRODUCTION

Early-onset neonatal sepsis occurs in roughly one in a thousand live births in high-income settings, and in a small proportion of those it is rapidly fatal or leaves permanent injury [1,2]. The clinical problem is that the infants who will become septic are not reliably distinguishable at birth from the very many who will not.

The response has been to treat generously. A categorical approach, in which any of a list of maternal risk factors triggers investigation and empirical antibiotics, has been standard for decades and reliably identifies most cases [3,4]. It also results in a substantial share of an entire birth cohort receiving intravenous antibiotics, separation from the mother, and interruption of feeding for a condition almost none of them has.

That exposure is not free. Early antibiotic exposure has been associated with disruption of the developing microbiome, with necrotising enterocolitis in preterm infants, and with later atopic and metabolic outcomes, and it carries the ordinary costs of cannulation, admission and interference with establishing breastfeeding [5–7]. Antimicrobial stewardship in the newborn nursery is therefore not merely an ecological concern.

A multivariable alternative combines a quantitative estimate of risk, derived from maternal factors, with the infant's clinical condition in the hours after birth, and reserves antibiotics for those above a stated threshold or those who appear unwell [8,9]. Implementation studies have reported substantial reductions in antibiotic use [10,11].

What such studies cannot readily provide is the counterfactual: the same infants managed both ways, with the true infection status of every one of them known. That is what simulation permits, and it allows a question that the comparative literature tends to leave implicit — not which strategy is better, but what exactly the threshold is deciding.

1.1 Objectives

We aimed to quantify the antibiotic exposure generated per case identified under each strategy; to characterise the trade-off across the range of plausible treatment thresholds; to determine how each strategy responds to the underlying prevalence of infection; and to describe the clinical appearance of infected infants not treated empirically at birth.

2. METHODS

2.1 Cohort

Figure 1 shows the structure. We simulated 200,000 births with gestational age, maternal group B streptococcal colonisation, adequacy of intrapartum antibiotic prophylaxis, duration of membrane rupture and maximum intrapartum temperature. True infection was generated from these factors, with the model intercept calibrated by bisection so that the realised prevalence matched a target of 0.8 per 1000; the achieved prevalence was 0.86 per 1000, giving 172 cases.

Each infant was assigned a clinical appearance at birth in three categories. Infected infants were far more likely to appear unwell but not uniformly so, reflecting the clinical reality that some infected newborns are initially well. In the simulated cohort 0.46% of all infants appeared clinically ill and 5.2% equivocal.

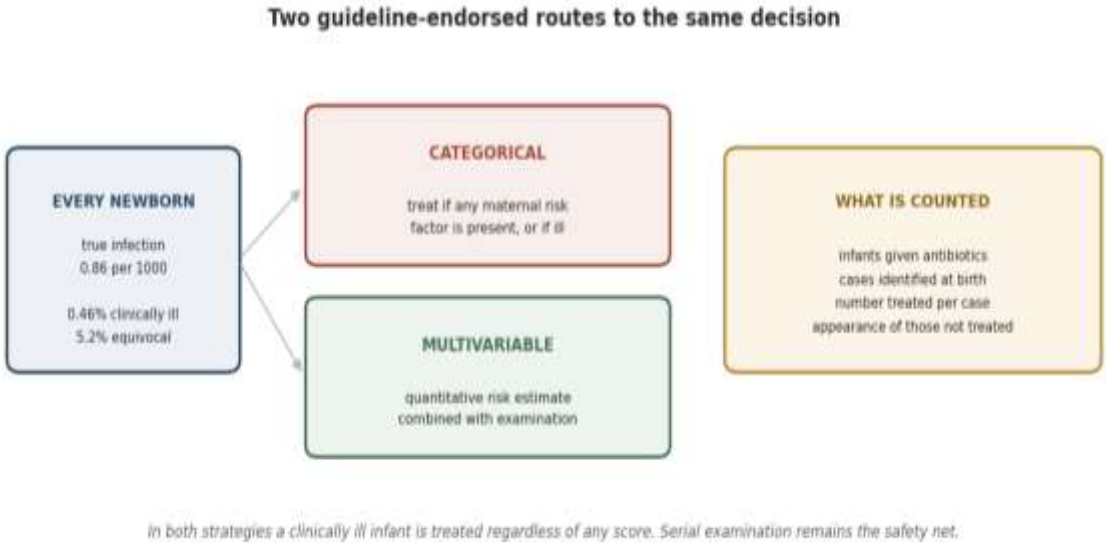

Figure 1. Cohort structure and the two decision routes. A clinically ill infant is treated under both strategies regardless of any score

2.2 The two strategies

The categorical strategy gave empirical antibiotics if any of four maternal risk factors was present — intrapartum fever, prolonged rupture of membranes, group B streptococcal colonisation without adequate prophylaxis, or preterm birth — or if the infant appeared clinically ill.

The multivariable strategy computed a risk estimate per 1000 births from the same maternal factors, with added noise representing the imperfection of any real model, and combined it with clinical appearance: a

clinically ill infant was treated regardless of the estimate, an infant with equivocal signs was treated at a lower threshold, and a well-appearing infant was treated only above the stated threshold. The base-case treatment threshold was 3 per 1000.

We wish to be explicit that both strategies treat the clinically ill infant unconditionally, and that neither replaces observation. The analysis concerns which well-appearing infants receive antibiotics before any sign has appeared, and nothing in it bears on the management of an infant who becomes unwell.

2.3 Outcomes

We report the proportion of infants receiving empirical antibiotics, the proportion having blood cultures taken, the number of true cases treated empirically at birth, sensitivity, and the number of infants treated per case identified. We then varied the treatment threshold and, separately, the true prevalence, and described the clinical appearance of infected infants not treated at birth.

Parameters are illustrative, chosen so that the resulting figures lie within the ranges reported in the implementation literature, and are stated in Table 1. Analyses used Python with NumPy; the complete script with all seeds accompanies this paper. All data are synthetic, no infants or records were involved, and institutional review board approval and informed consent were not applicable.

Table 1. Cohort and model parameters

Component	Specification	Rationale
Births simulated	200,000	Enough to observe a rare outcome stably
True infection prevalence	0.86 per 1000	Calibrated by bisection to the target
Group B streptococcal colonisation	22% of mothers	Within reported screening prevalence
Adequate prophylaxis if colonised	78%	Reflects incomplete delivery of prophylaxis
Clinical appearance	Three categories, assigned by infection status	Infected infants more often unwell, but not all
Categorical trigger	Any of four maternal risk factors, or clinically ill	The conventional rule
Multivariable threshold	3 per 1000 in the base case	Within the range used in practice
Model imprecision	Noise added to the risk estimate	No real model is perfectly calibrated

3. RESULTS

3.1 Exposure per case identified

Table 2 and Figure 2 compare the strategies. The categorical rule gave antibiotics to 21.23% of the cohort — 42,457 infants — and identified 125 of the 172 true cases, a sensitivity of 0.727. That is 340 infants treated for each case identified at birth.

The multivariable approach gave antibiotics to 4.45% — 8,896 infants — and identified 121 cases, a sensitivity of 0.703 and 74 infants per case. Exposure was 4.8-fold lower for a difference of 4 cases identified empirically at birth.

Both figures for infants treated per case are large, and that is the more important observation. Even the more selective strategy treated 74 infants to identify one infection at birth, because the condition is rare and no combination of maternal factors and initial appearance identifies it closely. The debate between strategies is a debate about whether that number should be 74 or 340, not about whether it can be small.

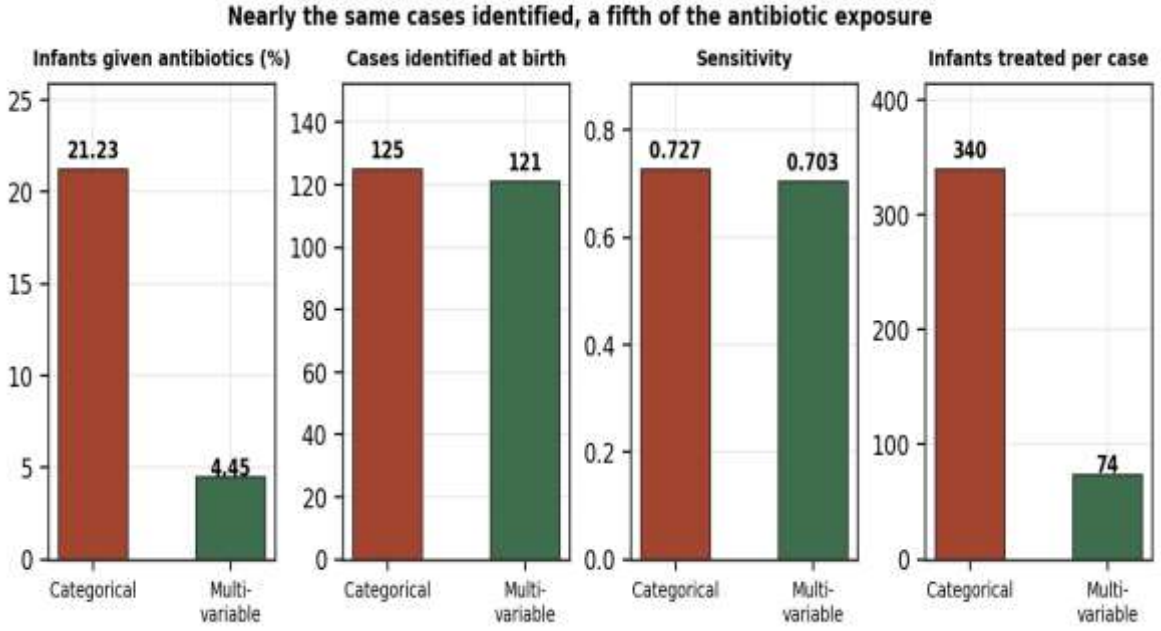

Figure 2. Antibiotic exposure, cases identified, sensitivity and infants treated per case under the two strategies

Table 2. Performance of the two strategies

Strategy	Infants treated (%)	Infants treated (n)	Cases identified at birth	Sensitivity	Treated per case
Categorical risk-factor approach	21.23	42,457	125	0.727	340
Multivariable risk with examination	4.45	8,896	121	0.703	74

True cases in the cohort: 172. Both strategies treat a clinically ill infant regardless of score.

3.2 What the threshold decides

Table 3 and Figures 3 and 4 vary the treatment threshold from 0.5 to 10 per 1000. At the lowest threshold, 59.2% of infants received antibiotics and 164 of 172 cases were identified at birth. At the highest, 0.65% received antibiotics and 97 cases were identified.

Figure 3 plots these as an efficiency frontier and locates the categorical rule on it. The categorical rule sits below the frontier: it treated 21.2% of infants for a sensitivity of 0.727, whereas a threshold of about 1.5 per 1000 achieved a higher sensitivity, 0.814, while treating fewer infants, 15.9%. On these figures the categorical rule is not a different point on the same trade-off; it is a less efficient way of making it.

Figure 4 states the trade in the terms a clinician and a parent would recognise: as the threshold rises the number of infants treated per case identified falls steeply, and the number of infected infants not started on antibiotics at birth rises. Neither curve tells anyone where to stand on it. That choice depends on how much antibiotic exposure a service and its families consider an acceptable price for identifying one infection some hours earlier, which is a judgement about values and not a quantity any analysis produces.

We would emphasise this because threshold recommendations are often presented as though they were derived. They are chosen. What analysis contributes is the exchange rate, not the decision.

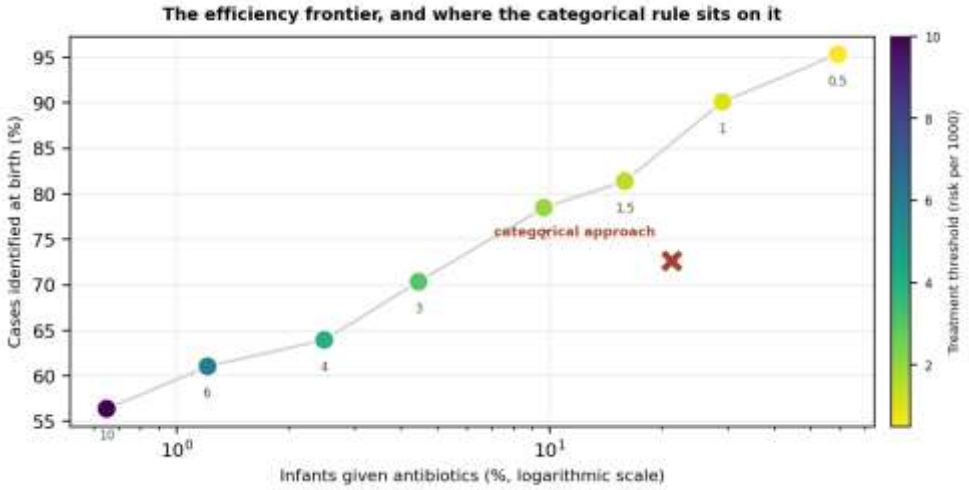

Figure 3. Cases identified against infants treated across treatment thresholds, with the categorical rule marked

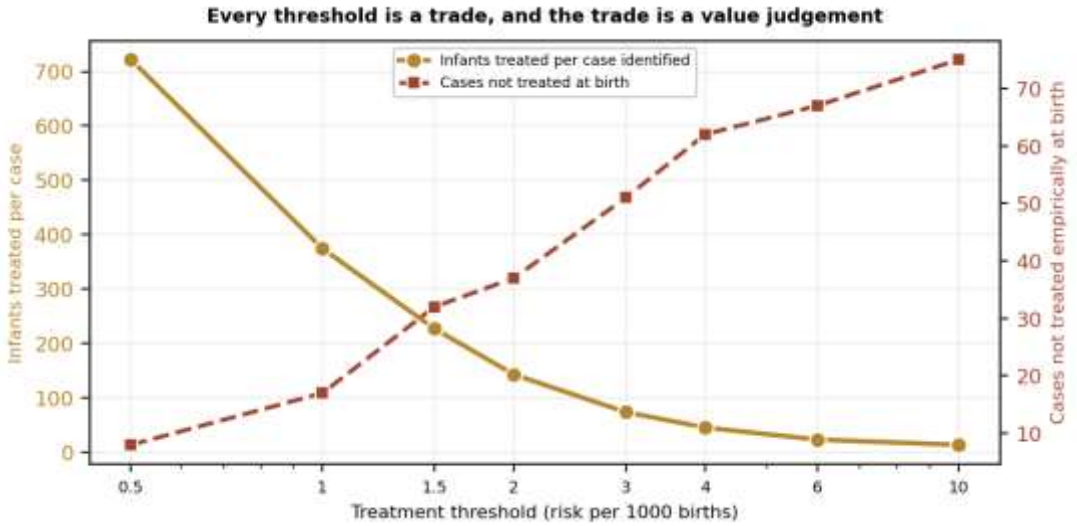

Figure 4. Infants treated per case identified, and cases not treated empirically at birth, across thresholds

Table 3. Treatment threshold sweep

Threshold (per 1000)	Infants treated (%)	Cases identified	Cases not treated at birth	Sensitivity	Treated per case
0.5	59.18	164	8	0.953	722
1.0	29.02	155	17	0.901	374
1.5	15.89	140	32	0.814	227
2.0	9.64	135	37	0.785	143
3.0	4.45	121	51	0.703	74
4.0	2.49	110	62	0.640	45
6.0	1.21	105	67	0.610	23
10.0	0.65	97	75	0.564	13

3.3 A categorical rule cannot see prevalence

Table 4 and Figure 5 vary the true prevalence of infection from 0.3 to 3.0 per 1000. The categorical rule gave antibiotics to between 21.18% and 21.26% of infants across that entire tenfold range — essentially a constant.

The multivariable approach scaled with the risk it faced, treating 0.78% at the lowest prevalence and 38.7% at the highest. The number treated per case fell for the categorical rule from 748 to 88 simply because cases became commoner, not because the rule did anything differently.

The reason is structural. A categorical rule fires on the presence of risk factors, and how common those risk factors are in a population is only loosely related to how much infection that population has. A unit with a high rate of prolonged membrane rupture and a low rate of infection will treat a large share of its babies and find almost nothing; a unit in the opposite situation will do the reverse. Neither can tell from its own antibiotic usage figures which situation it is in.

This also means the exposure a categorical rule generates is not a clinical choice a service has made. It is a consequence of its obstetric case mix, arrived at without anyone deciding it.

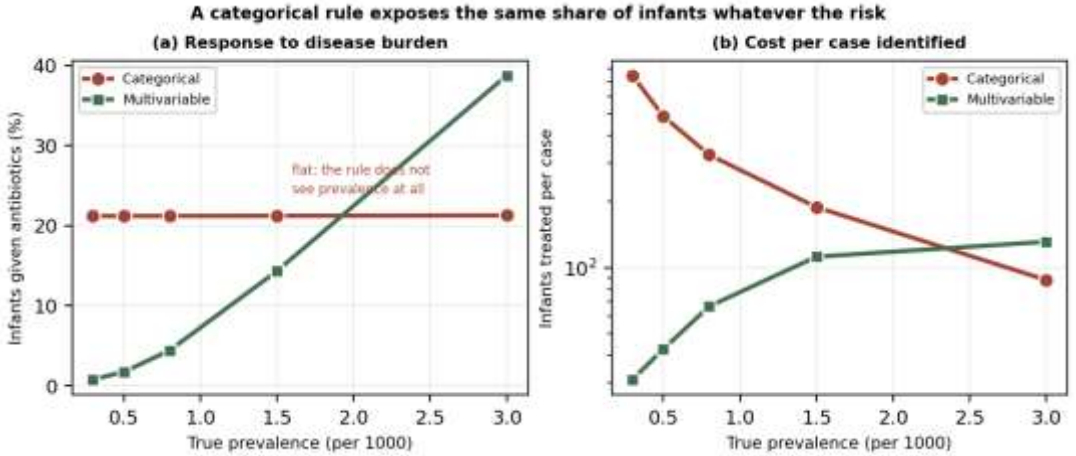

Figure 5. Response of each strategy to the underlying prevalence of infection

Table 4. Sensitivity to true prevalence

True prevalence (per 1000)	Categorical: treated (%)	Categorical: per case	Multivariable: treated (%)	Multivariable: per case	Ratio of exposure
0.30	21.18	748	0.78	31	27.3
0.50	21.19	489	1.71	43	12.4
0.80	**21.19**	**326**	**4.40**	**67**	**4.8**
1.50	21.21	189	14.31	112	1.5
3.00	21.26	88	38.73	131	0.5

3.4 Who is not treated at birth

Table 5 and Figure 6 describe the infected infants not given antibiotics at birth. Under the categorical rule there were 47, of whom 13 well appearing, 34 were had equivocal signs and 0 were clinically ill. Under the multivariable approach there were 51, comprising 24 well appearing, 27 equivocal and 0 clinically ill.

No clinically ill infected infant went untreated under either strategy. This is not a finding about the risk models; it follows from both strategies treating an ill infant unconditionally, which is how they are designed and how they are used. It is worth stating explicitly because the risk of these approaches is sometimes discussed as though a score might override an examination, and in neither strategy does it.

The infants not treated at birth were, in both strategies, those who looked well or equivocal at the time of the decision. Whether they come to harm depends entirely on whether they are seen again and treated

when signs appear. The safety of any reduction in empirical treatment therefore rests on the reliability of serial observation and on the arrangements for escalation, not on the accuracy of the risk estimate, and a service that reduces empirical antibiotic use without strengthening observation has changed only the first half of the strategy.

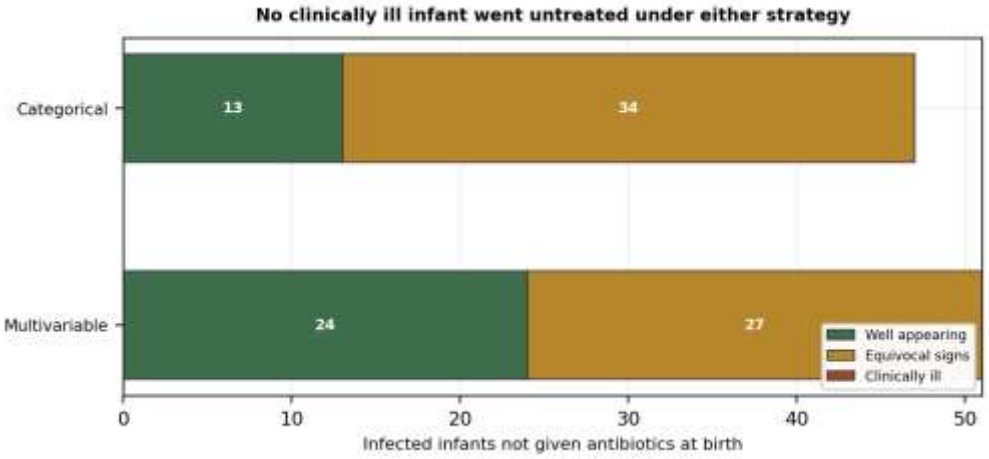

Figure 6. Clinical appearance of infected infants not given antibiotics at birth, by strategy

Table 5. Clinical appearance of infected infants not treated empirically at birth

Strategy	Total	Well appearing	Equivocal	Clinically ill
Categorical	47	13	34	0
Multivariable	51	24	27	0

3.5 Cultures and downstream investigation

Table 6 reports blood culture use, which follows the same pattern as antibiotic exposure. The categorical strategy cultured 21.23% of infants and the multivariable strategy 30.30%.

Culture volume matters independently of antibiotics. A blood culture in a newborn requires a painful procedure, generates a result that is frequently contaminated, and commits a proportion of infants to continued antibiotics pending a result that will be negative. Reporting antibiotic days without reporting cultures understates what a strategy costs.

Table 6. Investigation burden.

Strategy	Infants cultured (%)	Infants treated (%)	Cultures per case identified
Categorical risk-factor approach	21.23	21.23	340
Multivariable risk with examination	30.30	4.45	501

4. DISCUSSION

4.1 Principal findings

Four findings follow. The two strategies differed 4.6-fold in infants treated per case identified, for a difference of 4 cases identified at birth. The categorical rule sat below the efficiency frontier: a multivariable threshold existed that identified more cases while treating fewer infants. A categorical rule treated a near-constant share of infants across a tenfold range of true prevalence. And no clinically ill infected infant went untreated under either strategy.

The unifying observation is that the quantity being decided is exposure, not detection. Both strategies identify most cases at birth and neither identifies all; what separates them by a factor of five is how many

uninfected infants are treated to achieve that. A comparison reported in terms of sensitivity alone conceals precisely the dimension on which they differ.

4.2 Relation to existing work

Categorical management based on maternal risk factors is long established and is credited with much of the fall in early-onset group B streptococcal disease, alongside intrapartum prophylaxis [1,3,4]. Multivariable risk estimation combined with clinical examination was developed to reduce the resulting exposure, and implementation studies across many units have reported substantial reductions in empirical antibiotic use without detectable increases in adverse outcome, although individual studies are underpowered for so rare an event [8–12]. Systematic reviews report the same direction with appropriate caution about the strength of the safety evidence [13,14].

This study adds the counterfactual that those studies cannot supply: the same infants, with true infection status known, managed both ways. Two of the findings seem to us to be new in emphasis rather than in kind — that the categorical rule is dominated rather than merely more conservative, and that its exposure is unresponsive to prevalence and therefore not a choice any service has made.

4.3 Implications

Figure 7 and Table 7 set out four recommendations. Two deserve comment.

Publish infants treated per case identified, alongside sensitivity. A service reporting only that its protocol identifies most cases has reported the easy half. The number of well infants who received antibiotics to achieve that is the quantity families, stewardship committees and neonatal services should be able to see, and every unit already holds the data to compute it.

Strengthen observation before reducing empirical treatment, not afterwards. Every infant this analysis leaves untreated at birth is well or equivocal at that moment, so the entire safety margin of a more selective strategy lies in whether deterioration is detected. A unit that adopts a lower-exposure strategy without first securing reliable serial examination, documented escalation criteria and adequate staffing has taken the benefit and not the precaution.

Figure 7. Proposed practice for services choosing between risk stratification strategies

Table 7. Recommendations

Recommendation	Addresses	Cost	Evidence here
Report infants treated per case identified	Sensitivity reported without its price	None; data already held	Section 3.1
State the threshold as a chosen value, not a derived one	A judgement presented as a calculation	None	Section 3.2
Audit exposure against local infection prevalence	A rule whose exposure is set by case mix	Linkage of usage to outcomes	Section 3.3
Secure serial observation before reducing treatment	The safety margin of a selective strategy	Staffing and protocol	Section 3.4
Report culture volume alongside antibiotic days	Investigation burden omitted from comparisons	None	Section 3.5
Treat any clinically ill infant regardless of score	A score mistaken for an override of examination	None	Section 3.4

4.4 Limitations

This is a simulation and its parameters are ours. Risk factor prevalences, the strength of their association with infection, and the distribution of clinical appearance were chosen so that the resulting figures lie within published ranges, not estimated from a dataset. The magnitudes follow from those choices; the structural findings — the dominance of the frontier and the prevalence-blindness of a categorical rule — follow from the form of the rules and are more robust.

The most consequential simplification is that clinical appearance is assessed once, at birth, and is a three-level variable. In practice examination is repeated over 24 to 48 hours, and an infant who is well at birth and unwell at six hours is identified by that process and not by any birth-time decision. Our model therefore understates the safety of every strategy, and understates it most for the more selective one, whose reliance on subsequent observation is greatest.

We modelled empirical treatment at birth and not its duration, so we cannot speak to antibiotic days, the commonest stewardship metric, nor to the practice of stopping at 36 to 48 hours on a negative culture, which substantially reduces total exposure under either strategy.

Infection was treated as a single entity. Organism, virulence, and the speed of deterioration vary, and a strategy that delays treatment in a fulminant infection is not equivalent to one that delays it in an indolent one. Our model has no time course and so cannot represent this, which is the respect in which it is least adequate to the clinical question.

Finally, we quantified exposure and detection, not harm. The weight to be attached to one infant treated unnecessarily against one infection treated some hours later is exactly what this analysis does not supply, and Section 3.2 argues that no analysis could.

5. CONCLUSION

In a simulated cohort of 200,000 births with 172 true infections, a categorical rule gave antibiotics to 21.2% of infants and identified 125 cases at birth; a multivariable approach combined with examination gave antibiotics to 4.4% and identified 121. The difference in exposure was 4.6-fold; the difference in cases identified was 4.

Across a tenfold range of true prevalence the categorical rule treated a near-constant share of infants, because it responds to how common risk factors are rather than to how common infection is. Its exposure is therefore a consequence of obstetric case mix rather than a decision anyone has taken.

The threshold in a multivariable approach is a decision, and it is a decision about how much antibiotic exposure is an acceptable price for identifying one infection some hours earlier. Analysis can supply the exchange rate and cannot supply the answer. What protected the ill infants in every scenario we modelled was not the score but the examination, and that is where the safety of any reduction in empirical treatment continues to rest.

Declarations

Ethical approval: Not applicable.

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Conflicts of interest: The authors declare that there are no conflicts of interest regarding the publication of this paper.

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions:

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Dr. Ayesha Sara	✓	✓		✓				✓		✓		✓	✓	✓

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

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