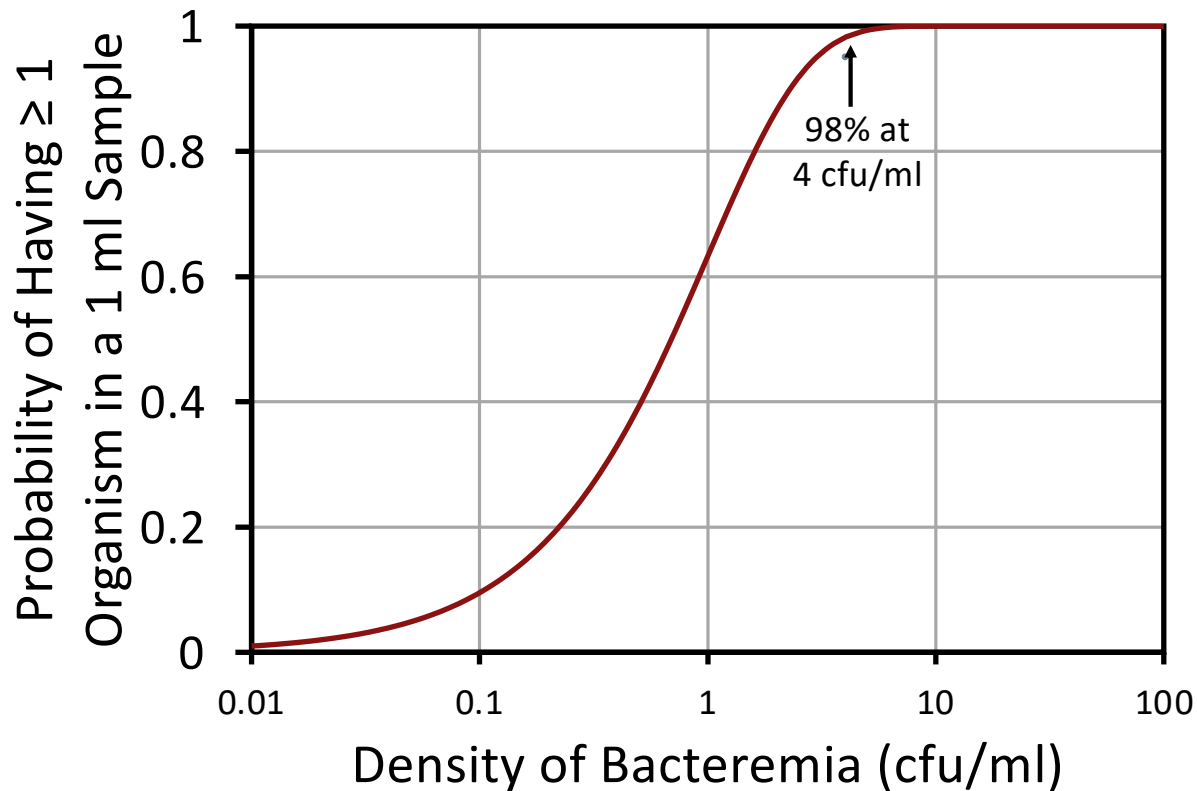


Rationale #5

“Neonatal blood cultures are notoriously insensitive.
This could be a false-negative result.”

Culture Negative Sepsis

Evidence for Adequacy of Culture Methods



The Poisson distribution predicts essential certainty of having at least 1 organism in a 1 ml inoculum if the density of bacteremia is ≥ 4 cfu/ml.

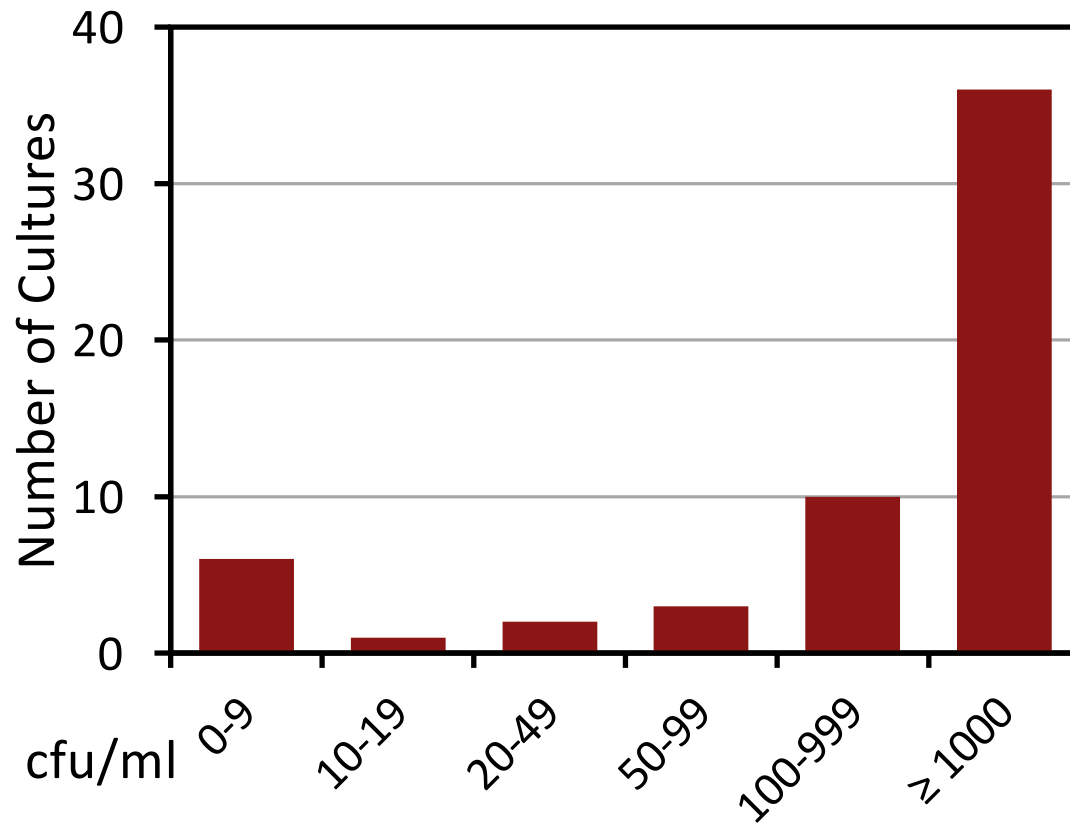
$$P[+] = 1 - e^{-\lambda}$$

where $\lambda = \text{cfu/ml}$

Arpi 1989, Schelonka 1996

Culture Negative Sepsis

Evidence for Adequacy of Culture Methods



Most infants with sepsis
have high density
bacteremia:
80% \geq 100 cfu/ml
90% \geq 10 cfu/ml

Culture Negative Sepsis

Modern blood culture methods reliably detect bacteremia at the levels seen in newborn infants with sepsis.

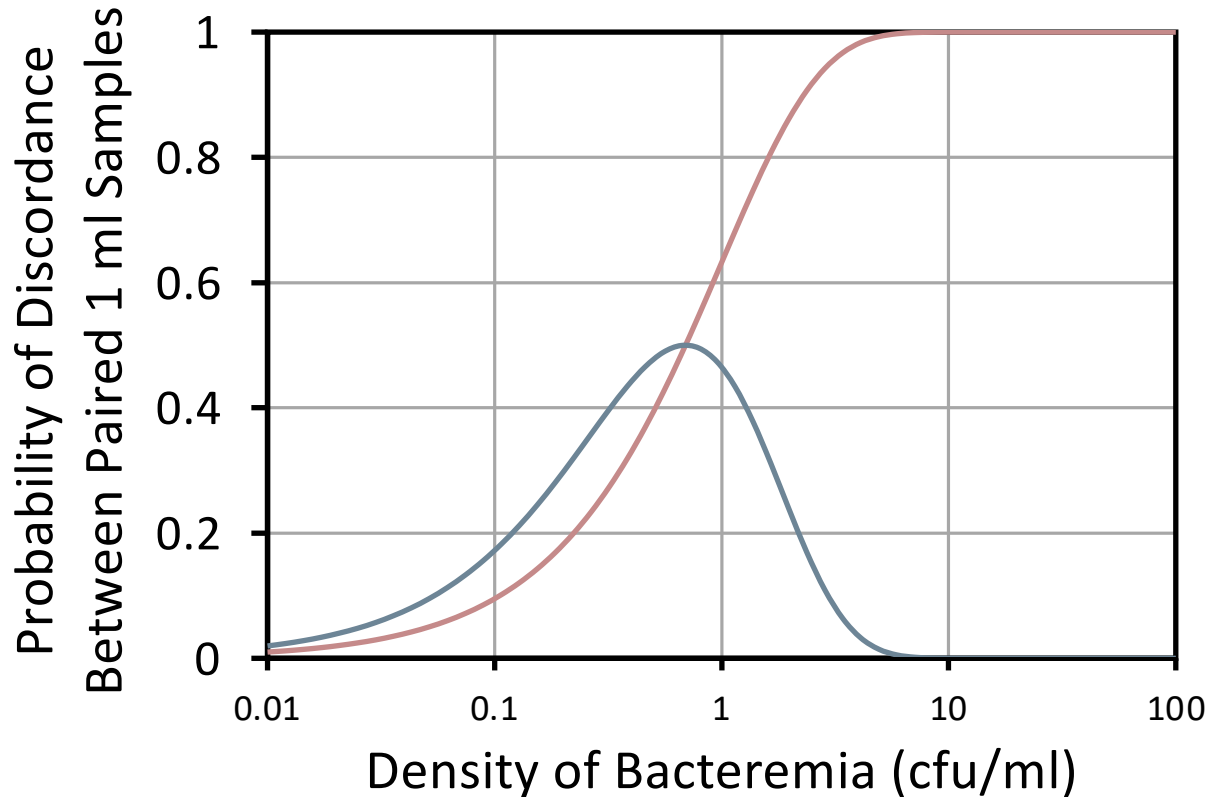
Rationale #6

“Saying that ultraslow density bacteremia – below the limits of detection – isn’t seen doesn’t mean it isn’t there.

It just means it isn’t detected using insensitive culture methods.”

Culture Negative Sepsis

Evidence for Adequacy of Culture Methods



> 45% of paired samples will be discordant at bacteremia densities between 0.42 and 1.07 cfu/ml.

The probability of observing no discordant pairs in a set of samples including at least 5 subjects with bacteremia at those densities is < 5%.

Adapted from Schelonka 1996

Culture Negative Sepsis

Evidence for Adequacy of Culture Methods Paired Neonatal Blood Cultures Are Rarely Discordant

		Paired Culture Results*	
		Site 2	
		Negative	Positive
Site 1	Negative	247	0
	Positive	0	22

* ≥ 1 ml per bottle

The high concordance of paired culture results implies that ultralow density bacteremia episodes must be very rare (< 2% of neonates who have blood cultures).

Culture Negative Sepsis

Evidence for Adequacy of Culture Methods Paired Adult Blood Cultures Are Often Discordant

		Paired Culture Results*	
		Tube 2	
		Negative	Positive
Tube 1	Negative	1545	25
	Positive	18	105

* most cases comparing 6.5-8 to 13-16 ml

The higher rate of discordant blood culture results reflects the **much higher rate of very low density bacteremia** (< 1 cfu/ml) in adults.

Significantly different from neonatal data (Sarkar) at $P = 0.008$.

Rationale #7

“The blood culture is only negative because of intrapartum antibiotic treatment.”

Culture Negative Sepsis

Effects of Intrapartum Antibiotic Exposure

Condition	OR for EOS (95% CI)
Preterm premature rupture of membranes	0.41 (0.21-0.81)
Chorioamnionitis	0.14 (0.04–0.54)
GBS colonization*	0.19 (0.07–0.53)

* OR for GBS EOS only

Intrapartum antibiotic treatment *reduces* the risk of neonatal bacteremia.

It is illogical to construe intrapartum treatment as a risk factor *for* sepsis.

“When cultures are sterile after adequate IAP, bacterial concentrations in the infant either have been reduced to ultralow concentrations or sterilized, neither of which require treatment.”

Benitz 1999, Cantey 2017