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## Reply



### To the Editor:

We agree with Dr Klingenberg that our study is open to potential bias due to missing data. We appreciate the chance to discuss this further.

The infants contributed from the 13 NICUs represent a variable proportion of the total number of admissions during the 3.5-year study period from each NICU. Nonetheless, they were included consecutively in one or several shorter periods. Because we were unable to obtain information on the number and basic characteristics of the missing infants within these periods, we refrained from analyzing or reporting this. Therefore, we acknowledge that some infants are missing in the dataset. The study was carried out by medical file review without central funding. The data extraction and goals for enrollment were developed prospectively. Part of the enrollment was done retrospectively, and we were not able to search long for missing files. However, the missing infants are unlikely to be missing at random; they are more likely to represent infants who were admitted for a shorter time, were transferred to other departments or hospitals, or were the subjects of people reviewing files—for example, infants who died early or who were transferred for surgery for necrotizing enterocolitis (NEC) elsewhere. For this to lead to systematic bias to occur (regardless of cause), it would have had to be associated with the administration (or recording) of early antibiotics as well as with NEC. We cannot posit good reasons why this should occur very often or in a biased fashion. Our data came from infants who were admitted to the NICU. Infants with birth weight >1500 g, considered too healthy for intensive care, and considered too immature for life support are not represented. Both groups likely did not receive antibiotics and did not get NEC.

We were also surprised by the 9% risk of NEC in the relatively mature group of infants who were admitted to

the NICU and did not receive early antibiotics. However, this number is the value that we have the least reason to doubt. Although NEC is not always a purely objective diagnosis, it is unlikely that the diagnosis was biased by a lack of early antibiotic use.

We are concerned with the overuse of antibiotics, so the motivation for the study was to look for clinically relevant complications to help clinicians. This was an unexpected finding—although we realize that others had data pointing in the same direction.

Finally, we want to emphasize that we do not believe that this question has been answered definitely. Rather, the question has been (re)opened, and many neonatal network datasets exist that can be used to test it again. We hope these data will become available. Furthermore, we hope that our results will motivate a search for potential mechanisms of preventing NEC. NEC remains a significant problem in neonatology and even appears to be increasing in extremely preterm infants in our own country.<sup>1</sup>

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