Critical Pertussis Among Infants—Many More Miles to Go!*

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Pertussis has been a vexing public health problem for decades. Robust infant and childhood pertussis immunization programs have resulted in dramatic reduction in morbidity and mortality, especially in industrialized countries. However, some of these countries have experienced a “pertussis resurgence” along with associated morbidity/mortality and consequent financial burden (1). In contrast, many developing countries continue to grapple with pertussis control through routine vaccination efforts and attempts to build effective surveillance systems (2, 3). Against this backdrop, significant additions to scientific literature on “critical” pertussis are of great interest to the global community.

In this issue of Pediatric Critical Care Medicine, Straney et al (4) presents the largest series to date, of infants with severe pertussis, with the stated objectives of calculating its incidence, exploring clinically relevant outcomes, and identifying risk-factors for mortality. Briefly, the authors searched records of 29 ICUs in Australia and New Zealand to identify infants with pertussis during the period 2002–2014. ICU admissions were compared to national-level surveillance data to calculate incidence. Markers of disease severity and outcomes in the participating ICUs were recorded to calculate final outcome, and a few well-recognized clinical characteristics were examined as “risk factors” for adverse outcome. From the report (4), it is unclear whether all the participating ICUs had uniform or similar admission criteria. Similarly, the clinical indications for initiating specific therapeutic strategies are also unclear.

Despite the commendable effort, the report (4) raises many questions. First, the title and aims of the study suggest that it is related to “severe” pertussis, without defining the term. However, the text shows that only infants admitted to the ICUs were included in the analysis. Previous authors have labeled pertussis requiring intensive care as “critical pertussis”; this term encompasses clinical indicators of disease severity and consequent need for intensive care, including apneic episodes, severe pneumonia, convulsions, and their associated complications (5, 6). The distinction between “severe” and “critical” pertussis is more than semantic because studying the former necessitates identifying severe cases (with specific definitions) from all the areas for patient care (not just the ICUs), such as emergency departments, neonatal care units, and perhaps even community health facilities. Therefore this study (4) deals with critical pertussis, not necessarily severe pertussis.

We believe that pediatric (and neonatal) intensivists would be primarily interested to learn more about 1) predictors of the need for intensive care; 2) appropriate timing of transfer to ICUs; 3) indication (and timing) of ventilation and other strategies; 4) outcome(s) of specific strategies used in the ICU (especially early detection of pulmonary hypertension, leukopenia reduction strategies [7, 8] such as exchange transfusion [9] or early extracorporeal membrane oxygenation [ECMO], N-acetyl cysteine lavage, etc [10]); 5) predictors of (un)favorable outcome(s); and 6) strategies to use limited resources efficaciously and effectively. In fact, some of these issues were raised previously also in this journal (11). However, these points remain largely unexplored in this study (4).

The inclusion criteria for pertussis in this study was the identification of registry codes associated with the disease (4). Infants whose records showed these codes as the principal, underlying, or associated diagnosis were included in the analysis. Thus confirmation of diagnosis was not mandatory, in contrast to some previous studies (5, 12). This means that some of the included infants could have had other clinical conditions (with or without pertussis). Further, heightened clinical suspicion during periods of outbreaks would translate to more infants being suspected with pertussis at all levels of healthcare, and consequently greater frequency of referral for intensive care. This could be the reason for the two- to three-fold leap in ICU admissions during 2009–2013 (4). The recent Global Pertussis Initiative has devised clinical definitions of pertussis in various age groups, but still includes laboratory criteria (13). Against this background, a subgroup analysis of laboratory confirmed pertussis cases could have enhanced the validity of some of the conclusions in this study (4).

The authors express “requirement” of intensive care whereas they mean “receipt of intensive care.” This is also not a semantic issue because the infants included in this analysis are the ones that “received” intensive care, whereas many more might have “required” it but did not receive (on account of resource limitation, delayed referral, and mortality prior to arrival to an ICU). Therefore, the data on proportion of infants requiring intensive care may not be entirely valid, unless readers can...
be assured that all infants eligible for intensive care actually received it.

The incidence of critical pertussis was calculated by dividing the number of ICU admissions by the total number of pertussis cases obtained from annual national surveillance data. Thus both the numerator and denominator included cases labeled as pertussis, without specifying the criteria for this. A recent report shows stark differences between data obtained through sentinel surveillance and routine surveillance (14). The former can identify two- to 12-fold greater number of cases, depending on the age-group under surveillance. If the surveillance (mentioned in this study) was a routine (passive) system, it would likely under-estimate the total number of pertussis cases although the number of critical cases is unlikely to change. In this scenario, the unchanged numerator and expanded denominator would point to a lower burden of critical pertussis than reported (4). If this is true, then the higher rate of ICU-admission (number of ICU admissions labeled as pertussis divided by the total number of ICU admissions) could merely reflect heightened sensitivity among clinicians and a consequent lower threshold for intensive care during the periods of national outbreaks.

Table 3 suggests that a significant number of mortalities occur very rapidly, giving little time to intervene (4). In such a scenario, it is vital for intensivists to identify characteristics associated with adverse outcome (to concentrate efforts and/or allocate scarce resources judiciously). Since 14 infants less than 60 days old died, but 192 survived; this was an excellent opportunity to conduct a case-control type of analysis matching fatal cases to survivors and identify factors associated with mortality. Instead, the investigators chose to highlight either known associations or markers of greater disease severity (4). The association of mortality with advanced support measures (such as ECMO and nitric oxide) merely suggests that the infants were either more sick or there was a time lag in transferring infants to centers where such interventions could be administered. This line of thought would likely explain why infants with inter-hospital transfers had greater need for ventilation and unfavorable outcome in this study.

On the brighter side, the latter part of the study period (2009–2014) was associated with better survival. But what contributed to this? Exploration of this important issue (for intensivists and patients) would have been very helpful. Could it be due to increase in PICUs, or better management protocols within ICUs, or shorter transit time to an ICU, or advanced technologies within ICUs, or simply a lower threshold for ICU admission during outbreaks? It would also be interesting to know whether the survival pattern varied among the participating ICUs. If yes, it would be helpful to undertake separate analyses of units with better survival and worse outcomes, comparing the pertussis-related mortality with the respective overall mortality. It is possible that “excess” mortality with pertussis may simply reflect overall mortality patterns in some units.

Finally, this study brings into focus the critical issue of protecting young infants from pertussis and lends support to strategy to vaccinate women earlier in pregnancy (15) with or without additional cocooning strategies (16).

REFERENCES