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Investment Long Overdue in Primary Studies of HIV Exposed Uninfected Infant Infectious Morbidity

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To The Editors,

The study by Pui-Ying Iroh Tam and colleagues published in the October 2018 issue of PIDJ hypothesized that “HIV exposed uninfected (HEU) children hospitalized with pneumonia will be more malnourished and have more severe disease than HIV-uninfected children [this should probably read HIV-unexposed children, as HEU children are HIV-uninfected], although the difference will not be as marked as for HIV-infected children.”[1] Given the central hypothesis relating to HEU children, we found it interesting that the cohort only included 25 HEU children compared to 26 HIV-infected children and 291 HIV-unexposed uninfected (HUU) children. It is also important for readers to note that children had to be aged 6–59 months to be eligible for inclusion in the two cohort studies from which this secondary analysis was drawn, thus excluding infants under 6 months of age. This is particularly important, as multiple studies have identified that the highest disparate risk of infectious morbidity for HEU infants occurs in the first six months of life compared to HUU infants, a window of vulnerability about which this study cannot comment [2,3]. Therefore, due to the sample size and eligibility criteria employed for this study it is not surprising that no association between HEU status and pneumonia-related mortality was observed. Furthermore, it is well-established that HEU infants experience a greater severity of manifestations of infectious diseases than HUU infants [2]. It is thus puzzling that the authors

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consider clinical markers of severity such as oxygen saturation and the Blantyre coma score on admission as confounders to the relationship between HIV exposure status and overall mortality. We would consider these clinical markers of severity to be on the causal pathway between HIV-exposure or HIV-infection status and mortality and thus not appropriate to adjust for in multivariable analysis for this specific hypothesis. Numerous well-designed studies have observed a slightly increased risk for all pneumonia but a substantially-increased risk for severe pneumonia and pneumonia-related mortality in HEU compared to HUU infants [4,5].

We urge investigators, when designing studies related to HEU infant and child infectious morbidity or mortality, to carefully consider the epidemiology that is emerging around this vulnerability in HEU infants. Globally 1.25 million HEU infants are born annually and they account for up to 25% of the total infant population in the highest HIV-burden countries.

Advancing the science to understand vulnerability to infectious diseases in this large population has been hampered by secondary analyses of studies designed primarily for another purpose. The study by Tam and colleagues is just one example. As we move beyond securing child survival to ensuring that all children thrive, investment in studies primarily designed and appropriately powered to evaluate pathways to morbidity and mortality in HEU compared to HUU infants and children in high HIV-burden countries is long overdue.

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