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RESEARCH ARTICLE

Hospital Volume and Mortality of Very Low-Birthweight Infants in South America

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Objective. To assess the effects of hospital volume of very low-birthweight (VLBW) infants on in-hospital mortality of VLBW and very preterm birth (VPB) infants in South America.

Data Sources/Study Setting. Birth-registry data for infants born in 1982–2008 at VLBW or very preterm in 66 hospitals in Argentina, Brazil, and Chile.

Design. Regression analyses that adjust for several individual-level demographic, socioeconomic, and health factors; hospital-level characteristics; and country-fixed effects are employed.

Data Collection/Extraction Methods. Physicians interviewed mothers before hospital discharge and abstracted hospital medical records using similar methods at all hospitals.

Principal Findings. Volume has significant nonlinear beneficial effects on VLBW and VPB in-hospital survival. The largest survival benefits—more than 80 percent decrease in mortality rates—are with volume increases from low to medium or medium-high levels (from ≤ 25 to 72 infants annually) with significantly lower incremental benefits thereafter. The cumulative volume effects are maximized at the 121–144 annual VLBW infant range—about 90 percent decrease in mortality rates compared to <25 VLBW infants annually.

Conclusions. Increasing the access of pregnancies at-risk of VLBW and VPB to medium- or high-volume hospitals up to 144 VLBW infants per year may substantially improve in-hospital infant survival in the study countries.

Key Words. Child and adolescent health, hospitals, maternal and perinatal care and outcomes, referrals and referral networks, quality of care/patient safety (measurement), pediatrics

The relationship between patient volume and hospital care quality has been a topic of considerable interest (Luft, Bunker, and Enthoven 1979; Halm, Lee, and Chassin 2002). The premise is that treating more patients with complex conditions increases the knowledge, efficiency, and quality of

health care providers in treating these patients. This question has significant implications for improving the outcomes of very low-birthweight (VLBW, <1500 g) or very preterm birth (VPB, <32 gestational weeks) infants who are at high mortality risk and have experienced lower survival gains with recent health care improvements than heavier and less preterm infants (Arias et al. 2003).

Several studies in the United States (Phibbs et al. 1996, 2007; Chung et al. 2010; Wehby et al. 2012) and other developed countries (Bartels et al. 2006) evaluate the effects of hospital VLBW infant volume on in-hospital mortality and generally find that higher volume reduces mortality risk. However, some studies find limited volume effects beyond low thresholds (Rogowski et al. 2004). Identifying the volume effects for high-risk infants has implications for regionalizing their hospital delivery and care as volume may become a quality indicator for consumers/insurers (Leapfrog Group 2011).

Hospital volume effects on VLBW infant survival have not been adequately investigated in less developed countries. To our knowledge, there is no published research that examines this question for South American countries. A major constraint has been the lack of adequate datasets. Identifying the hospital volume effects on the survival of high-risk infants specifically for South American countries is essential for improving their health care systems as the volume-effect estimates for developed countries may not apply in less developed settings, where hospitals typically have lower staffing levels, less advanced technology, and less specialized professionals than developed countries and where advanced/specialized care may be available only in large urban areas. Furthermore, health care standards are likely to vary between developed and less developed countries. Such differences in hospital structures and care processes may result in differences in hospital volume effects between developed and less developed settings. Another gap in the literature

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has been the inadequate evaluation of how volume effects might change at very high volumes. In this study, we evaluate the VLBW volume effects on VLBW and VPB mortality in hospitals in Argentina, Brazil, and Chile. We employ a unique dataset that, to our knowledge, may be one of the few readily available data sources to address this question for these countries. We also investigate closely the nonlinearity in volume effects within a wide volume range.

METHODS

Data Source

The data are from the Latin American Collaborative Study of Congenital Anomalies (ECLAMC), a program for epidemiological investigations and surveillance of birth defects in South America (Castilla and Orioli 2004). ECLAMC involves voluntary collaboration with a large network of hospitals and physicians. The ECLAMC-affiliated physicians obtain data for all infants born with birth defects in their hospitals through maternal interviews before hospital discharge and hospital record abstraction on prenatal risk factors, socioeconomics, birth outcomes, and hospital discharge-status using the *same questionnaires* and *subject-identification approaches* across *all hospitals*. Furthermore, the physicians identify and enroll in ECLAMC live born nonmalformed infants matched one-to-one with the affected infants by gender, hospital, and date of birth, and obtain *similar data* on these infants. The nonmalformed group represents a 2–3 percent random sample of all nonmalformed births at ECLAMC-affiliated hospitals, and participation is very high (more than 95 percent). In addition, ECLAMC obtains monthly data on the numbers of *total* births at each hospital by live birth status, and beginning in 1982, by birthweight status. Several infant health studies have employed ECLAMC data (e.g., Lopez Camelo et al. 2006; Wehby et al. 2009a,b,c).

ECLAMC-affiliated hospitals serve geographically and socioeconomically diverse communities, which enhances the sample's representativeness. As reported below, the study sample has significant variation in socioeconomic, demographic, and health characteristics. Several of these characteristics cannot be directly compared with their population-level counterparts as these are not readily available. However, for available population-level measures, the sample is generally comparable to the population (Wehby, Castilla, and Lopez-Camelo 2010). While it is impossible to completely evaluate the sample representativeness, the sample socioeconomic and geographic

diversity and the lack of significant differences with measured population characteristics suggest that the ECLAMC sample is representative of large percentages of the study populations. Furthermore, on practicality grounds, we are unaware of an alternative data source that allows a similar evaluation with detailed measures of prenatal and postnatal characteristics.

Study Sample

The study includes *all* live born and nonmalformed infants enrolled in 66 ECLAMC hospitals between 1982 and 2008 in Argentina, Brazil, and Chile. Due to ECLAMC's enrollment criteria, the sample only includes infants born in the study hospitals. As shown below, we adjust for the birth period to account for changes in care standards and practices over time and for changes in hospital participation in ECLAMC over time. We focus on infants without birth defects given the very high mortality rates for several severe birth defects, the limited effectiveness of hospital care in reducing these mortality rates, and the extensive variation in mortality risks and treatment protocols by birth defect type and severity. The total ECLAMC sample consists of 54,286 live born infants without birth defects. Of these, 679 infants are born at VLBW (<1,500 g), and 1,487 infants are VPB (<32 gestational weeks). We limit the sample to infants with a minimum 500-g birthweight and 19.5-week gestational age given that most infants below these thresholds are usually stillbirths. Gestational age was measured as the period between the date of birth and the date of the last menstrual period as reported by the mother at the interview with ECLAMC physicians before hospital discharge after delivery. This measure has been used in several of the above-referenced infant health studies using ECLAMC data.

In-Hospital Mortality

The study outcome is in-hospital mortality before discharge after birth. Some infants who remained hospitalized after birth at the time when the physicians reported the data to ECLAMC have not been continuously followed after that to document their final discharge status. ECLAMC requires the physicians to report within the first 2 weeks of each month data on all infants enrolled in the previous month. For example, physicians are asked to report within the first 2 weeks of April data on all infants enrolled during March. Physicians are expected to follow up on infants who were still hospitalized at the time of this initial data transfer to document their final discharge status and several

complete these follow-ups. However, as the main objective of the ECLAMC program is the clinical and epidemiological investigation of birth defects, there is no predefined period for following up infants who were still hospitalized. Therefore, the follow-up duration may vary among ECLAMC-physicians and infants, and some infants who were still hospitalized at the last follow-up have no final discharge status (discharged alive or died in the hospital). One concern is that hospital volume may relate to unobserved final discharge status if ECLAMC physicians in lower or higher volume hospitals have systematically different follow-up periods. Also, mortality may be "delayed" in higher volume hospitals, resulting in overestimated volume benefits if ignored. We describe below how we address this limitation.

The primary outcome is a binary indicator of in-hospital death at the last ECLAMC-physician's follow-up of the infant. For cases with available mortality dates (about half), death occurred between 1 and 39 days of life, suggesting that death was measured at least throughout the neonatal period. For infants who have been discharged alive, hospital length of stay (available for about half) ranged from 1 to 124 days, which also suggests follow-up at least throughout the neonatal period. Therefore, the primary outcome represents "early" in-hospital mortality relative to being discharged alive or remaining hospitalized at the last physician's follow-up.

To account for the undefined final discharge status (or censoring) for infants still hospitalized at the last follow-up, we employ several sensitivity analyses to evaluate the extent to which censoring affects the study inference about volume effects. The first sensitivity analysis uses a three-category outcome that includes censored infants in a separate category from the two groups with final discharge status (dead or discharged alive) and estimates the volume effects on these three categories. This formally acknowledges the potential volume effects on censoring. We find that most of the volume effects on mortality with this three-category outcome measure are virtually similar to those with the main binary mortality outcome. In a second sensitivity analysis, we estimate the volume effects excluding censored infants and observe virtually similar results for most volume effects. In addition, we define specific follow-up periods and measure mortality within the first 7, 10, and 28 days of life, with a separate model employed for each period. To accomplish this, we employ a four-category multinomial outcome: (1) discharged alive or survived the follow-up period (7, 10, or 28 days); (2) death within the follow-up period; (3) death before hospital discharge after birth with unknown death date; and (4) still hospitalized at last follow-up (censoring). As we describe below, we find significant volume effects on mortality within these defined neonatal

periods that are larger than but similar in pattern to those found for in-hospital mortality at any time before discharge. Furthermore, hospital volume has no effects on the other categories of this multinomial dependent variable (death with unknown date or still hospitalized at last follow-up versus discharged alive or survived defined period). These evaluations provide some assurance that there are no systematic differences in ECLAMC-physicians' follow-up that significantly confound the general inference about volume effects in this dataset.

Volume

For each child, we measure hospital volume by the number of VLBW infants born alive in the same hospital during the 12 months before the child's birth. We avoid using a calendar-year volume measure (fixed for all infants born in the same year) as this ignores seasonal volume fluctuations and inappropriately assigns future volumes to children born earlier in the calendar year. Using the hospital monthly total of live births at or below 1500 g, we are able to measure, for each infant, the VLBW volume described above. More than 75 percent of the sample infants have complete VLBW volume data for every month and require no imputation. When hospital birth totals are missing for certain months of the 12 months (19 percent of the sample), we estimate the total VLBW births for the missing months based on the average of the months with observed data. About 66 percent of these cases have complete data for at least 6 months. We also exclude data for months when more than 10 percent of the hospital live births have missing birthweight (about 6 percent of the sample; affecting 1 month for 83 percent of these cases), and estimate the total VLBW live births based on the months with complete data.

Given that the estimated total annual volumes for infants with incomplete 12-month series data are based on at least 6 months of complete (nonimputed) data and that VLBW hospital delivery rates are generally stable and vary little over a monthly basis, the volume estimates are expected to be appropriate. However, imputing may introduce some measurement error, which may bias the volume effect toward 0. The large and significant volume effects presented below suggest that such measurement error has very little effect, if any, on the study results. Furthermore, as a sensitivity analysis, we re-estimate the volume effects excluding cases with imputed volume data and find generally similar results as described below.

Hospital volume may have nonlinear effects on in-hospital infant mortality. The benefits of added knowledge/experience with higher volume may

increase first (with volume) due to specialization but eventually decrease because of fixed resources and crowding effects (constraints of space, technology, or physician/staff time/attention) or because of reduced communication between the hospital's staff per at-risk infant. In the presence of such constraints, additional volume may not improve infant's survival. To account for such potential nonlinearity in volume effects, we include multiple indicators for the sample's VLBW volume ranges. In addition to estimating the effects of each volume range, we test for whether the effects are significantly different between all the volume ranges. To evaluate multiple nonlinear effects through the entire observed volume range, the main model includes indicators for ranges of annual hospital volumes increasing by 24 VLBW (or VPB) infants (with the minimum category including 24 infants annually or 2 infants per month). The only exceptions are the two largest volume categories, which have wider ranges to maintain a minimum frequency of about 5 percent. However, given that very few hospitals are observed in the largest volume categories, we employ a sensitivity analysis where cutoffs are based on either volume tertiles (i.e., tertiles of the number of VLBW infants) or quartiles and find overall a similar pattern of results. We also find similar results using a continuous volume measure with a squared term to capture nonlinear effects.

Statistical Analysis

We assess the VLBW volume effects on in-hospital mortality adjusting for all observed health, socioeconomic, demographic, and hospital characteristics that are conceptually relevant for infant mortality and for self-selection into hospital volume based on pregnancy complications and maternal/physicians' expectations for fetal/infant health. Maternal factors include education, employment/occupational status, age, indicators for acute illnesses during pregnancy such as flu and chronic illnesses such as diabetes or hypertension, prenatal medication use, fertility history, and cesarean delivery. Infant characteristics include child's race/ethnicity, gender, and birthweight indicators. Gestational age indicators are included in the VLBW mortality function (insignificant in the VPB mortality function). No other potential individual-level confounders are observed in the dataset. Hospital characteristics include ownership, funding/payment systems, type, and university affiliation.

To our knowledge, there are no established systems for the neonatal intensive care level in the study hospitals that can be adjusted for. However, a large recent study using United States data has reported significant VLBW

hospital volume effects on in-hospital mortality independent of the neonatal intensive care level, which had insignificant effects when adjusted for volume (Chung et al. 2010). Furthermore, higher VLBW volume may motivate and enable hospitals to further acquire advanced neonatal care technology, which in turn may affect mortality rates. In that case, identifying the total volume effect on mortality requires excluding neonatal care technology from the model as adjusting for it would result in estimating a partial volume effect on mortality (i.e., an effect other than through technology). Therefore, both theory and previous empirical evidence (Chung et al. 2010) suggest that it is unlikely that our study estimates of the total VLBW volume effects on mortality will be significantly biased by the lack of neonatal care technology measures. The model also adjusts for the birth period and country. Table 1 lists the distributions of study variables.

We estimate the mortality function using logistic regression with Huber-type variance estimation that accounts for sample clustering across the study hospitals (Wooldridge 2002). We alternatively estimate this model using random-effect and general estimating equations logistic regressions and find virtually identical results (results available from the authors upon request). We find no evidence of collinearity issues—volume indicators have variance inflation factors below 4. We estimate the three-category discharge-status function (alive, death, continued hospitalization) using multinomial logistic regression with hospital-clustered standard errors.

RESULTS

Volume and In-Hospital Mortality

The in-hospital VLBW and VPB mortality rates are 21.7 and 10.8 percent, respectively (Table 1). About 8, 17, and 29 percent of the VLBW sample are born in hospitals with 25 or fewer, 26–48, 49–96, 97–144, and >144 annual VLBW infants, respectively. Figure 1 shows the unadjusted VLBW and VPB mortality rates by volume. VLBW mortality rates range from 12.5 percent for the 73–97 infant volume to 41.1 percent for the 25 or fewer infant volume. VPB mortality rates range from 6.1 percent for the 73–97 infant volume to 17.4 percent for the >192 infant volume. The graph indicates nonlinear relationships between volume and VLBW and VPB mortality rates, which continuously decrease and reach their minimum at the 73–97 infant volume, then increase beyond that. A Cochran-Armitage-type test of linear volume effects is rejected ($p = .002$) for both VLBW and VPB mortality.

Table 1: Distribution of Study Variables

	Very Low-Birthweight Babies % or Mean (SD)	*Very Preterm Birth Babies % or Mean (SD)*
In-hospital mortality	21.7	10.8
Total annual volume of <25 VLBW infants*	8.1	9.4
Total annual volume of 25–48 VLBW infants	16.7	17.4
Total annual volume of 49–72 VLBW infants	11.7	12.0
Total annual volume of 73–96 VLBW infants	17.7	18.3
Total annual volume of 97–120 VLBW infants	17.6	17.3
Total annual volume of 121–144 VLBW infants	11.7	11.7
Total annual volume of 145–192 VLBW infants	10.5	9.1
Total annual volume of >192 VLBW infants	6.0	4.8
Hospital is privately owned	2.2	1.7
Hospital only provides unfunded/unpaid care*	46.4	48.3
Hospital only accepts insurance or out of pocket payments	12.4	11.5
Hospital accepts insurance/out of pocket payment and provides unfunded/ unpaid care	41.2	40.2
Maternity hospital	22.9	22.0
Hospital affiliated with university	72.0	67.6
Acute illnesses	43.4	35.6
Chronic illnesses	20.4	16.0
Difficulty in conception	9.4	8.9
Number of live births before child	1.5 (2.2)	1.7(2.3)
Number of stillbirths/miscarriages	0.4 (1.0)	0.3(0.8)
Medicine use during pregnancy	67.1	62.0
Cesarean section delivery	55.6	37.4
Maternal education of incomplete primary school	28.6	32.7
Maternal education of complete primary school	23.6	22.1
Maternal education of incomplete secondary school	21.1	23.7
Maternal education of complete secondary school*	19	17.2
Mother attended university	7.7	4.3
Medium-/high-skill maternal occupation	13.3	11.2
Maternal age of 19 years or younger	20.5	25.2
Maternal age between 20 and 25 years	28.9	31.2
Maternal age between 26 and 34 years*	34.7	30.7
Maternal age of 35 years and older	15.9	12.9
Male infant	55.0	52.8
Infant of African ancestry	28.6	25.0
Infant of native ancestry	58.3	61.6
Birthweight of 500–699 g	6.5	2.8

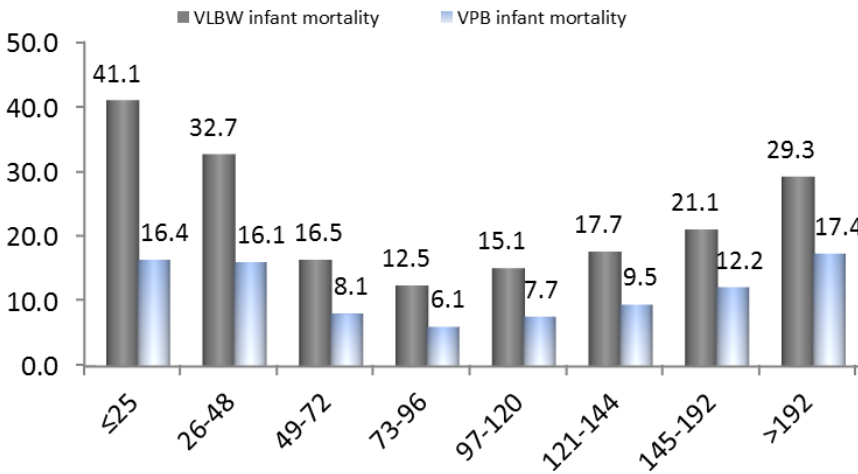
continued

Table 1. *Continued*

	Very Low-Birthweight Babies % or Mean (SD)	*Very Preterm Birth Babies % or Mean (SD)*
Birthweight of 700–899 g	15.0	6.6
Birthweight of 900–1,099 g	20.1	8.4
Birthweight of 1,100–1,299 g	26.1	8.7
Birthweight of 1,300–1,499 g*	32.3	73.5
Gestational age of 20–24 weeks	5.5	7.9
Gestational age of 24.1–28 weeks	27.0	24.3
Gestational age of 28.1–30 weeks	21.7	25.6
Gestational age of 30.1–32 weeks	20.5	42.1
Gestational age > 32 weeks*	25.3	–
Birth in years 1982–1990*	14.3	13.5
Birth in years 1991–1995	18.1	18.3
Birth in years 1996–2000	24.8	25.1
Birth in years 2001–2008	42.8	43.1
Argentina*	29.9	39.9
Brazil	55.2	48.2
Chile	14.9	17.9

Note. The table reports the distributions of the study variables in the VLBW and VPB infant samples.
*indicates the reference (excluded) category in the regressions.

Figure 1: Hospital VLBW Volume and Unadjusted In-Hospital Mortality Rates



Note. The figure shows the crude (unadjusted) mortality rates for VLBW and VPB infants by hospital VLBW volume.

Table 2: Odds Ratios of the Logit Regression of In-Hospital Death before Discharge after Birth

	Very Low-Birthweight Babies	*Very Preterm Birth Babies*
Total annual volume of 25–48 VLBW infants	0.48 [0.16, 1.45]	0.57 [0.26, 1.29]
Total annual volume of 49–72 VLBW infants	0.14 [0.04, 0.49]***	0.18 [0.06, 0.57]***
Total annual volume of 73–96 VLBW infants	0.20 [0.06, 0.64]***	0.24 [0.07, 0.79]**
Total annual volume of 97–120 VLBW infants	0.12 [0.03, 0.45]***	0.16 [0.05, 0.52]***
Total annual volume of 121–144 VLBW infants	0.07 [0.01, 0.36]***	0.10 [0.03, 0.38]***
Total annual volume of 145–192 VLBW infants	0.22 [0.06, 0.76]**	0.37 [0.11, 1.23]
Total annual volume of >192 VLBW infants	0.29 [0.09, 0.89]**	0.22 [0.07, 0.69]***
Hospital is privately owned	0.22 [0.04, 1.22]*	0.20 [0.04, 0.97]**
Hospital only accepts insurance or out of pocket payments	0.82 [0.28, 2.38]	0.94 [0.33, 2.66]
Hospital accepts insurance/out of pocket payment and provides unfunded/unpaid care	1.21 [0.66, 2.23]	1.36 [0.66, 2.81]
Maternity hospital	2.95 [1.73, 5.02]***	3.30 [1.88, 5.78]***
Hospital affiliated with university	2.12 [1.08, 4.15]**	2.22 [1.11, 4.46]**
Acute illnesses	1.14 [0.67, 1.93]	0.83 [0.45, 1.53]
Chronic illnesses	0.56 [0.23, 1.42]	0.67 [0.31, 1.48]
Difficulty in conception	0.61 [0.27, 1.38]	0.59 [0.31, 1.14]
Number of live births before child	0.94 [0.82, 1.08]	0.94 [0.83, 1.06]
Number of stillbirths/miscarriages	1.19 [0.89, 1.59]	1.31 [1.03, 1.65]**
Medicine use during pregnancy	0.68 [0.38, 1.21]	1.04 [0.59, 1.82]
Cesarean section delivery	1.12 [0.73, 1.73]	1.39 [0.89, 2.15]
Maternal education of incomplete primary school	2.83 [0.87, 9.19]*	1.64 [0.54, 4.97]
Maternal education of complete primary school	1.46 [0.44, 4.82]	1.60 [0.63, 4.07]
Maternal education of incomplete secondary school	1.62 [0.52, 5.09]	1.58 [0.58, 4.27]
Mother attended university	0.89 [0.19, 4.25]	0.94 [0.23, 3.77]
Medium-/high-skill maternal occupation	0.61 [0.19, 2.01]	0.78 [0.26, 2.31]
Maternal age of 19 years or younger	1.74 [0.64, 4.70]	2.22 [1.11, 4.43]**
Maternal age between 20 and 25 years	1.03 [0.39, 2.69]	1.02 [0.51, 2.05]
Maternal age of 35 years and older	1.66 [0.72, 3.79]	1.73 [0.79, 3.78]
Male infant	1.29 [0.89, 1.86]	1.50 [0.98, 2.31]*

continued

Table 2. *Continued*

	Very Low-Birthweight Babies	*Very Preterm Birth Babies*
Infant of African ancestry	1.08 [0.38, 3.03]	1.15 [0.47, 2.80]
Infant of native ancestry	0.65 [0.22, 1.90]	0.77 [0.34, 1.73]
Birthweight of 500–699 g	43.92 [11.70, 164.87]***	210.21 [83.38, 529.95]***
Birthweight of 700–899 g	11.39 [5.57, 23.30]***	67.09 [37.86, 118.86]***
Birthweight of 900–1,099 g	2.59 [1.22, 5.49]**	17.85 [10.08, 31.59]***
Birthweight of 1,100–1,299 g	2.51 [1.22, 5.16]**	12.46 [6.89, 22.53]***
Gestational age of 20–24 weeks	6.16 [1.25, 30.45]**	
Gestational age of 24.1–28 weeks	8.69 [3.52, 21.43]***	
Gestational age of 28.1–30 weeks	6.90 [2.84, 16.75]***	
Gestational age of 30.1–32 weeks	5.46 [1.95, 15.31]***	
year_91_95	1.22 [0.53, 2.84]	1.45 [0.61, 3.48]
year_96_00	0.52 [0.19, 1.43]	0.59 [0.23, 1.56]
year_01_08	0.42 [0.17, 1.03]*	0.42 [0.17, 1.01]*
Brazil	0.20 [0.08, 0.47]***	0.26 [0.12, 0.56]***
Chile	0.23 [0.09, 0.59]***	0.19 [0.07, 0.50]***
Sample size	678	1,434
Pseudo R^2	0.406	0.446
Area under ROC curve	0.8999	0.9183

Note. 95% confidence intervals of the odds ratios in brackets. The reference (excluded) categories are listed in Table 1.
*$p < .1$,
**$p < .05$,
***$p < .01$.

Table 2 reports the regression results for VLBW and VPB mortality. The regressions have good fit (pseudo *R*-squared of 0.41–0.45; Hosmer-Lemeshow test *p*-values of .33–.52). Model specification tests of omitted variables do not reject the used specifications (*p*-values of .65–.81).

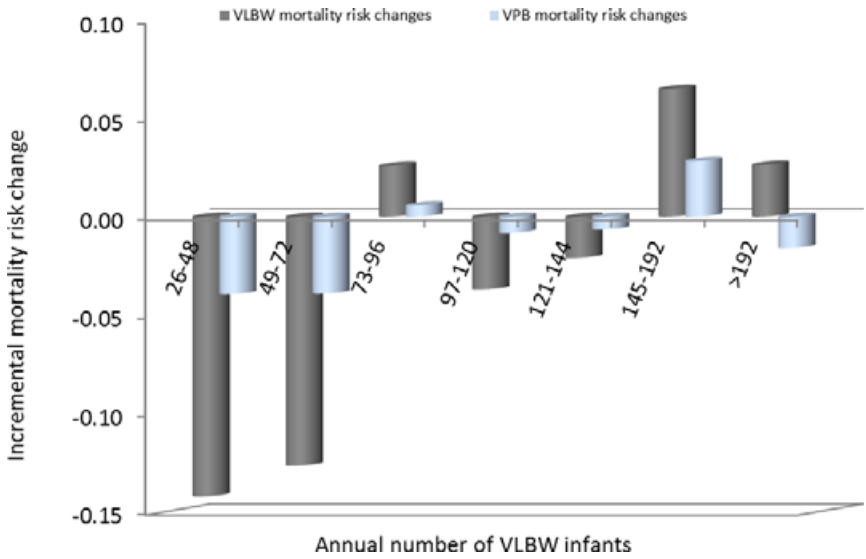
The VLBW and VPB mortality risks decrease significantly with VLBW volume. However, volume has nonlinear effects on VLBW mortality, with the volume effects—relative to very low volume—first increasing overall and becoming largest for the 121–144 annual infant volume, after which the effects decrease, but remain significant. Compared with a volume of 25 or fewer infants, higher volumes reduce VLBW mortality odds significantly by 86, 80, 88, 93, 78, and 71 percent for volume ranges of 49–72, 73–96, 97–120, 121–144, 145–192, and >192 annual VLBW infants, respectively (all effects are statistically significant). VLBW mortality odds also decrease by about half with an increase in annual VLBW hospital volume from 25 or fewer to 26–48 infants ($p = .19$). The effects are significantly different between the volume ranges ($p < .0001$).

The volume effects on VPB mortality are generally comparable to those on VLBW mortality and have overall a similar nonlinear trend. The effects are also significantly different between the volume ranges ($p = .0012$).

To evaluate the nonlinear mortality changes with volume effects, we estimate the incremental VLBW mortality changes with increasing volume thresholds. These are estimated from the logistic regression by successively differencing, between consecutive volume ranges, the mortality risk changes with each volume range (relative to the reference volume of 25 or fewer infants), holding other model covariates constant at their means.

Figure 2 shows these incremental mortality changes by volume. The incremental VLBW survival gains are largest with volume increases from low- to medium- or medium-high-volume thresholds—between 26 to 72 VLBW infants. Mortality decreases by more than 10 percentage points with volume increase from ≤ 25 to 26–48 infants (statistically insignificant), and from the latter to 49–73 infants (statistically significant). Lower incremental survival gains (3 percentage-point VLBW mortality decrease) are observed with increases from medium- or medium-high to high-volume ranges (between 73–

Figure 2: Incremental Mortality Risk Change with Increasing Hospital VLBW Infant Volume



Note. The figure shows the incremental changes in mortality with volume changes as predicted from the regressions listed in Table 2.

96 and 121–144 infants). Increasing volume beyond this range results in incremental survival loss for VLBW infants by about 3–5 percentage points with each successive increase to the 145–192 and >192 infant volumes. An overall similar pattern is observed for VPB infants, except that VPB mortality decreases slightly with volume increases from 145–192 to >192 infants (Figure 2).

Sensitivity Analyses

The volume effects on in-hospital mortality anytime before hospital discharge after birth using a three-category outcome that accounts for undefined final discharge status using multinomial logistic regression are listed in Supporting Information Appendix Table S1. Volume has no effects on continuous hospitalization for VLBW infants, and its effects on VLBW mortality are virtually similar to those for the binary mortality outcome, except at very high volumes (>144 VLBW infants) where effects are smaller and insignificant. Furthermore, hospital volume has no significant effect on undefined final discharge status (censoring). This can be further seen in Appendix Table S2, which lists the censoring rates by hospital volume. For VPB infants, the two largest volume ranges are associated with increased censoring compared with the lowest volume category (Tables S1 and S2). However, volume has significant effects on VPB mortality that are virtually similar to those for the binary mortality outcome through the 121–144 infant volume, beyond which the volume effects become insignificant and smaller.[1]

The volume effects on the binary outcome for mortality anytime before hospital discharge excluding infants with undefined final discharge status are listed in Appendix Table S3. These effects are generally comparable to those of the primary mortality outcome model and the three-category outcome models. The >192 infant volume effect on VPB mortality is marginally significant.

Large decreases in hospital mortality within defined periods of 7, 10, and 28 days after birth with increasing hospital volume are estimated from the multinomial logit models for the four category-dependent variable accounting for undefined final discharge status and death with unknown dates (results reported in Appendix Table S4 for the VLBW sample). These volume effects are larger than those for in-hospital mortality anytime before discharge after birth, but they follow a similar nonlinear pattern with incremental effects first increasing with volume but eventually decreasing. The larger volume effects on very early hospital mortality is not surprising given that volume may be associated with only a short extension in survival for some infants. Volume

has no effect on censoring or mortality without specified dates compared with discharge alive or surviving the specified periods in the VLBW sample. Some volume ranges have significant effects on these two outcomes in the VPB sample, but the pattern of volume effects on survival within the defined periods is similar to that ignoring censoring.[2] As a whole, these results provide some assurance of no major bias in the volume-effect estimates due to censoring.

As mentioned above, we evaluate other volume cutoffs and measures. Using indicators for either tertiles or quartiles of the number of VLBW infants, we find a similar pattern of results to those from the main model with more volume categories. Also, using a continuous volume measure with a squared term, we find that mortality decreases at an increasing rate with volume, also indicating that volume has diminishing marginal effects on survival. These results are summarized in Appendix Table S5. Finally, we re-estimate the volume effects using the main model specification only for the sample without imputed annual volume and find overall similar effects to those for the whole sample (results summarized in Appendix Table S6).

DISCUSSION

The study finds significant beneficial effects of hospital volume increases from low (≤ 25 infants annually) to medium or medium-high (72 infants annually) or high levels (144 infants annually) on reducing VLBW and VPB in-hospital mortality in the study countries. The largest incremental survival gains occur with volume increases from very low to medium levels (from ≤ 25 to 72 infants annually). There are significantly smaller survival gains with volume increases beyond these threshold and potential survival losses with volume increases beyond 144 infants. To our knowledge, there has been no specific evaluation of nonlinearity in volume effects at very high thresholds in previous studies.

The study is the first to assess the effects of VLBW volume on in-hospital mortality in South American populations using a unique sample that has significant demographic, socioeconomic, and geographic diversity, suggesting that it is well representative of large proportions of the study birth populations. The results are particularly relevant for less developed countries, given the high VLBW mortality rates in hospitals with low volumes, which are more than twice as high as in developed countries. For example, the mortality rate of infants born in the study hospitals with less than 25 VLBW infants annually is 41 percent, compared to about 17.1 percent in California hospitals in

1997–2002 (Phibbs et al. 1996, 2007; Bartels et al. 2006; Chung et al. 2010). The high mortality risks at very low-volume hospitals in the study countries emphasize the importance of developing policies that reduce the rates of delivering VLBW infants at these hospitals.

While the study has several strengths, some study limitations warrant discussion. One limitation is that we are unable to completely evaluate the extent to which the ECLAMC sample represents the whole infant populations in the study countries due to the lack of readily accessible population-level data. However, as described above, there is significant geographic diversity and variation in demographic and socioeconomic characteristics in the study sample, which enhance its representativeness. A related issue is that there are no readily available data to compare the neonatal intensive care levels between the ECLAMC hospitals and other hospitals in the study countries, in part due to the lack of a standardized system and data on neonatal care level (to our knowledge). Nonetheless, the extensive variation in volume and other observed characteristics between the study hospitals suggests that they are representative of a large proportion of the hospitals in the study countries.

In developed countries, higher risk pregnancies are generally referred into higher hospital volumes, which may attenuate the volume effects when ignored. The study models include several theoretically relevant variables and confounders, which may in-part account for any potential self-selection into hospital volume based on fetal and maternal health risks and pregnancy progress. Furthermore, there is no consistent pattern of selection of higher risk pregnancies into higher volumes based on observed confounders in the study sample (Tables S7 and S8 in the Appendix list the distributions of the study variables by hospital volume). However, it is possible that there are additional unobservable risk factors that affect self-selection and that may attenuate the volume effects especially for very high volumes, which show negative incremental survival gains compared with lower volumes and become insignificant when accounting for continuous hospitalization status.

One limitation is the censoring of the in-hospital mortality outcome for the group of infants who were still hospitalized at the last observation. We evaluate this issue using multiple approaches and find overall that this has no effects on the main results and study implications. Also, we have no data on admission to and length of stay in intensive neonatal care units. While this does not limit the estimation of the total hospital volume effects on mortality, this information would be useful to evaluate the process through which higher volume reduces mortality. We leave this question to future studies when such data become available.

The positive volume effects are generally consistent with findings from other populations (Phibbs et al. 1996, 2007; Bartels et al. 2006; Chung et al. 2010). However, we cannot directly compare all the estimated volume effects with previous studies due to differences in volume distributions and the nonlinear volume effects. Furthermore, there are no previous studies of volume effects on VLBW mortality in South American populations to compare with. The study sample is smaller than those of other population studies. However, it provides adequate variation to evaluate the volume effects. The sample includes a small number of very high-volume hospitals (see Appendix Tables S7 and S8). However, to our knowledge, these hospitals have no unobserved special characteristics that are confounding their volume effects. A related issue is that ECLAMC provides mortality and prenatal data only on a subset of births in the ECLAMC-affiliated hospitals. However, this limitation mainly relates to sample size and less to representativeness, as ECLAMC imposes no selection criteria that bias sample representativeness. VLBW infants form a small percentage of the birth population (about 1–2 percent), making it extremely challenging to identify a larger sample without the existence of national-level birth-registry and hospital-discharge datasets. On practicality grounds, the ECLAMC sample is, to our knowledge, one of few data resources that allow studying volume effects on VLBW and VPB mortality for the study populations.

The study findings support regionalized care for at-risk pregnancies. However, in less developed countries where large populations have limited access to high-volume providers typically located in highly urban areas, care regionalization may leave those nonurban residing mothers with high patient travel/time costs. Furthermore, high-volume providers in highly urban settings may already be operating on the flat-of-the-curve with minimal survival gains and even potential losses with increasing volume. The study finds that large survival returns in less urban areas may be achieved by increasing the access of at-risk pregnancies to hospitals with annual volumes of 49–72 VLBW infants. Additional smaller survival gains may be achieved at high levels up to 144 infants annually.

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NOTES

1. Hospital ownership, accepted payment systems, type, and university affiliation are not predictive of censoring status, with the exception of the hospital only accepting insurance or out of pocket payments being marginally and negatively related to censoring in the VLBW sample ($p = .088$).
2. Detailed results for these sensitivity analyses for the VPB sample are available from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Appendix SA1: Author Matrix.

Table S1. Multinomial Logit Odds Ratios for Volume Effects on Hospital Discharge-Status after Birth.

Table S2. Censoring Rates by Hospital Volume.

Table S3. Odds Ratios for Volume Effects on In-Hospital Death before Discharge after Birth Excluding Infants with Continued Hospitalization Status.

Table S4. Multinomial Logit Odds Ratios for Volume Effects on Hospital Discharge Status after Birth in the VLBW Sample.

Table S5. Effects of Alternative Volume Measures on In-Hospital Death before Discharge after Birth.

Table S6. Odds Ratios for Volume Effects on In-Hospital Death before Discharge after Birth Excluding Infants with Imputed Volume Measures.

Table S7. Distribution of Study Variables by Hospital Volume in the VLBW Infant Sample.

Table S8. Distribution of Study Variables by Hospital Volume in the VPB Infant Sample.