CRD summary
The authors concluded that very low birth weight and very preterm infants born in lower level hospitals were at significantly greater risk of neonatal or pre-discharge mortality. This was generally a well-conducted piece of research. The authors’ conclusions reflect the available evidence, but the poor quality of the studies and potential for bias should be borne in mind.

Authors’ objectives
To assess the effect of hospital level at birth and neonatal or pre-discharge mortality in very low birth weight and very preterm infants.

Searching
MEDLINE, CINAHL and EMBASE were searched between 1976 and May 2010 for publications in English. Search terms were reported. Published reference lists and references of obtained articles were searched for additional studies.

Study selection
Randomised controlled trials (RCTs), prospective and retrospective cohort studies and case-control studies that compared live-born very low birth weight (≤1,500g) and very preterm (at least 32 weeks’ gestation) infants born at level III facilities versus births at lower level of care facilities were eligible for inclusion. Outcomes of interest were neonatal mortality (death up to 28 days after live birth) or pre-discharge/in-hospital mortality (death of continuously hospitalised infant before discharge). Eligible studies were required to report data to permit meta-analysis.

Most of the included studies were conducted in USA; others were in Canada, Ghana, Israel, Australia and Europe. Hospitals in designated geographic regions were categorised based on the level of perinatal services provided: level I (basic uncomplicated neonatal care), level II (provision of care for moderately ill infants) and level III (equipped to care for serious neonatal illnesses and abnormalities, which included very low-birth-weight infants).

Two reviewers screened studies for inclusion. It was unclear how discrepancies were resolved.

Assessment of study quality
Three reviewers independently assessed the quality of the included studies according to level of adjustment for confounding and description of designated level of care and/or hospital care capabilities. Studies were categorised as insufficient quality (lack of adjustment for confounding and lack of hospital details), adequate quality (adjustment for at least two confounding variables and some hospital details) and high quality (adjustment for confounding and clear details on hospital level and capabilities).

Data extraction
Two reviewers independently extracted the number (%) of events to calculate adjusted or unadjusted odds ratios (ORs) and 95% confidence intervals (CIs). Outcome data on populations defined by birth weight were extracted separately to those defined by gestational age. In studies that compared infants at more than two hospital levels, the highest reported level of hospital being compared with level III care was included. Where the same population was used in different publications, the highest quality data were included. Authors were not contacted for additional information where data were missing or unclear. Discrepancies were resolved through referral to a third reviewer.

Methods of synthesis
A random-effects model was used to combine odds ratios and 95% confidence intervals, weighted by sample size. Statistical heterogeneity was assessed using the Q statistic.
Results were stratified by study quality (adequate and high-quality studies), for the smallest very low-birth-weight infants (≤1,000g) and very preterm infants. Subgroup analyses were undertaken based on study design, use of population-based or non-population-based data, data source, USA or study or elsewhere, outcome variables, birth weight range, inclusion of infants smaller than 500g, publication date and extent of control for confounding. Sensitivity analysis was undertaken by removal of one study at a time.

Publication bias was assessed using the Egger test and funnel plot.

**Results of the review**

Forty-one studies (n reported as 114,244 in the text, but calculated as 110,244 from the tables; range 29 to 27,191) were included in the review: one RCT; seven prospective cohort studies; 32 retrospective cohort studies; and one case-control. Four studies were rated as high quality, eight as adequate quality and 29 as insufficient quality.

The association between hospital level for very low birth-weight infants and mortality did not change over time.

Very low birth weight infants born in level I or II hospitals showed an increase in neonatal/pre-discharge mortality than infants born in level III hospitals (adjusted OR 1.62, 95% CI 1.44 to 1.83). Stratification by study quality showed similar findings (nine studies). There was evidence of statistical heterogeneity for both analyses (p<0.001).

The smallest very low birth weight infants born in level I or II hospitals showed significantly higher odds of neonatal and/or pre-discharge mortality compared to those born in level III hospitals (adjusted OR 1.80, 95% CI 1.31 to 2.46; five studies). There was evidence of statistical heterogeneity (p<0.001).

Similarly, very preterm infants born in lower level hospitals had greater odds of neonatal and/or pre-discharge mortality (adjusted OR 1.55, 95% CI 1.21 to 1.98; four studies). Subgroup analyses in very preterm infants by study quality showed similar findings (3 studies). There was no evidence of statistical heterogeneity for either comparison.

Subgroup analyses showed potential sources of heterogeneity based on level of adjustment for confounding. More extensively controlled studies showed no statistical heterogeneity. Sensitivity analysis did not significantly alter the results.

There was some potential for publication bias in very preterm studies (p=0.05).

**Authors’ conclusions**

Very low birth weight and very preterm infants born in level I or II hospitals were at significantly greater risk of neonatal or pre-discharge mortality.

**CRD commentary**

The review question and inclusion criteria were clearly defined. A number of electronic databases and one other appropriate source were searched. Studies were restricted to those published in English, so language bias may have been introduced. No attempts were made to locate unpublished studies, so potentially relevant studies may have been missed (acknowledged by the authors). Assessment of publication bias showed some potential for evidence of bias. The authors went some way to assess study quality and this was taken into account in the analyses, but the quality of most studies was unclear. The authors acknowledged that there were limitations with study quality. Each stage of the review process was performed in duplicate, which reduced potential for reviewer error and bias. Appropriate methods were used to combine the studies and investigate statistical heterogeneity. This was generally a well-conducted piece of research and the authors’ conclusions reflect the available evidence, but the poor quality of the studies and potential for bias should be borne in mind.

**Implications of the review for practice and research**

**Practice:** The authors stated that improved systems were needed in regions where high levels of very low birth weight and very preterm infants are born in lower level facilities.

**Research:** The authors stated the future research must thoroughly report hospital-level details and use appropriate
adjustment for confounding to achieve accurate effect estimates. Future research should explore the effect of hospital volume, obstetrical level and infants that continued to receive lower level hospital care after birth and include other outcome measures such as long-term infant morbidity and foetal and maternal mortality.

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