Estimated Number of Infants Detected and Missed by Critical Congenital Heart Defect Screening

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**abstract**

**BACKGROUND AND OBJECTIVES:** In 2011, the US Secretary of Health and Human Services recommended universal screening of newborns for critical congenital heart defects (CCHDs), yet few estimates of the number of infants with CCHDs likely to be detected through universal screening exist. Our objective was to estimate the number of infants with nonsyndromic CCHDs in the United States likely to be detected (true positives) and missed (false negatives) through universal newborn CCHD screening.

**METHODS:** We developed a simulation model based on estimates of birth prevalence, prenatal diagnosis, late detection, and sensitivity of newborn CCHD screening through pulse oximetry to estimate the number of true-positive and false-negative nonsyndromic cases of the 7 primary and 5 secondary CCHD screening targets identified through screening.

**RESULTS:** We estimated that 875 (95% uncertainty interval [UI]: 705–1060) US infants with nonsyndromic CCHDs, including 470 (95% UI: 360–585) infants with primary CCHD screening targets, will be detected annually through newborn CCHD screening. An additional 880 (UI: 700–1080) false-negative screenings, including 280 (95% UI: 195–385) among primary screening targets, are expected. We estimated that similar numbers of CCHDs would be detected under scenarios comparing “lower” (~19%) and “higher” (~41%) than current prenatal detection prevalences.

**CONCLUSIONS:** A substantial number of nonsyndromic CCHD cases are likely to be detected through universal CCHD screening; however, an equal number of false-negative screenings, primarily among secondary targets of screening, are likely to occur. Future efforts should document the true impact of CCHD screening in practice.

**WHAT'S KNOWN ON THIS SUBJECT:** Newborn screening for critical congenital heart defects (CCHDs) has been implemented in many hospitals, yet there is uncertainty about the number of infants with CCHDs that might be detected through universal implementation of newborn CCHD screening in the United States.

**WHAT THIS STUDY ADDS:** We estimated that ~875 infants with CCHDs might be detected, and ~880 missed, annually through universal CCHD screening in the United States. Increases in prenatal diagnosis are unlikely to substantially impact the number of infants detected through CCHD screening.

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Dr Ailes conceptualized and designed the study, acquired the data, carried out the analysis and interpretation of the data, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Gilboa, Honein, and Oster conceptualized and designed the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.


DOI: 10.1542/peds.2014-3662

Accepted for publication Mar 6, 2015
Congenital heart defects (CHDs) affect ∼8 per 1000 births and ∼25% are considered critical congenital heart defects (CCHDs). In 2011 the US Secretary of Health and Human Services recommended adding CCHDs to the newborn Recommended Uniform Screening Panel. Subsequently, screening for CCHDs through pulse oximetry, used to supplement standard clinical evaluation and monitoring of newborns, has been implemented in many hospitals. Screening protocols vary with regard to the age of the newborn at screening and the use of pre- and/or postductal oxygen saturation measurements. The American Academy of Pediatrics (AAP), the American Heart Association (AHA), and others recommend screening infants at 24 to 48 hours of life with consideration of both pre- and postductal measurements.

Estimates of the impact of CCHD screening differ. Differences in prenatal diagnosis and “late” detection (i.e., CCHD diagnosis after birth hospital discharge or after 3 days of life) by CCHD type and geographic location might contribute to the observed variation. Another potential contributor is the sensitivity of the pulse oximetry screening test; although the overall sensitivity is estimated to be 76%, it varies considerably by CCHD type, ranging from 36% to 100%.

Estimating the number of infants potentially detected (“true positives”) and missed (“false negatives”) through universal CCHD screening must incorporate 3 key sources of variability: (1) the birth prevalence of the specific CCHD; (2) the prenatal diagnosis prevalence, both across CCHD types and geographic region; and (3) the sensitivity of CCHD screening for different CCHD types. This study incorporated these elements into a simulation model to estimate the number of true-positive and false-negative CCHD cases in the United States likely to result from CCHD screening through pulse oximetry.

METHODS
We included the 7 CCHDs considered to be “primary” targets of screening: hypoplastic left heart syndrome (HLHS), pulmonary atresia, dextro-transposition of the great arteries (d-TGA), truncus arteriosus, tricuspid atresia, tetralogy of Fallot (TOF), and total anomalous pulmonary venous return (TAPVR). We also included the 5 “secondary” targets of CCHD screening: coarctation of the aorta (COA), double-outlet right ventricle, Ebstein anomaly, interrupted aortic arch (IAA), and single ventricle. Although critical aortic and pulmonary stenoses are also typically considered CCHDs, we lacked complete data on lesion severity. To calculate estimates for “all CCHDs” by summing across the specific CCHD estimates, we created a “multiple CCHDs” category including those cases with multiple CCHD diagnoses, such that no case was counted more than once. We restricted the analysis to infants with CCHDs diagnosed before 1 year of life. To better reflect the population of infants eligible for CCHD screening, all analyses were restricted to live-born infants and, for consistency across data sources, restricted to infants without chromosomal abnormalities (“nonsyndromic”).

Live-Birth Prevalence
We simulated a 2012 birth cohort of infants with nonsyndromic CCHDs by using data from the Metropolitan Atlanta Congenital Defects Program (MACDP), an active surveillance system for major birth defects in metropolitan Atlanta, Georgia. Surveillance is conducted for infants, fetuses, and stillbirths >20 weeks’ gestational age with major birth defects identified before 6 years of age. Trained abstractors visit birth hospitals, pediatric hospitals, specialty clinics, and perinatal offices to identify and abstract clinical and demographic information on potential cases. CHD cases are classified by clinicians with expertise in pediatric cardiology. For our analysis, we updated the analysis by Oster et al to calculate the 2000–2005 live-birth prevalence of the 12 selected CCHD types.

Frequency of Prenatal Diagnosis
Prenatal diagnosis was estimated by using data from the National Birth Defects Prevention Study (NBDPS), a multisite case-control study of risk factors for select major birth defects, including CCHDs. Cases were identified through birth defects surveillance systems in 10 US sites; infants with recognized or strongly suspected single-gene disorders or chromosomal abnormalities were excluded. Trained abstractors reviewed medical records of infants/fetuses with CCHDs and, to be included in the study, CCHD cases had to be confirmed by echocardiography, cardiac catheterization, surgery, or autopsy. Prenatally diagnosed cases were included only if confirmed by autopsy or by a clinician with expertise in pediatric cardiology. CCHD type(s) were assigned by physicians with specialized training in clinical genetics or pediatric cardiology. We defined prenatal diagnosis as (1) a maternal report of a prenatal diagnosis of a CHD (as had been done in a previous analysis) and/or (2) clinical record of a fetal echocardiography before the date of birth. Then, for each CCHD type, we calculated the 2000–2005 prenatal diagnosis prevalence.

Frequency of Late Detection
NBDPS data were also used to estimate the prevalence of “late” CCHD detection. Previously, we categorized infants with echocardiography or autopsy.
information as having “timely” CCHD detection if their first documented echocardiography was within 3 days of birth and as having “late” CCHD detection if their first echocardiography (or autopsy) occurred after the third day of life. Here, we modified the analysis slightly to be restricted to infants without a prenatal diagnosis (as defined above). We calculated the 2000–2005 late detection prevalence among live-born infants without a prenatal diagnosis.

**Sensitivity of Newborn CCHD Screening Through Pulse Oximetry**

We obtained CCHD-specific estimates of the sensitivity of screening through pulse oximetry from a review by Prudhoe et al, which used mutually exclusive CCHD categories but did not provide estimates for Ebstein anomaly or “multiple CCHDs.” We summed the number of cases reported to be detected through CCHD screening using pulse oximetry and the total number of cases screened, across all secondary screening targets, to obtain an estimate of screening sensitivity for Ebstein anomaly, and across all CCHDs, to obtain an estimate for multiple CCHDs.

**Analysis**

For each CCHD, we estimated the number of true-positive and false-negative cases resulting from CCHD screening through pulse oximetry (Fig 1). To account for uncertainty in our birth prevalence, prenatal diagnosis, late detection, and CCHD screening sensitivity for each CCHD type, we used normal distributions based on the reported estimated means and SEs for these variables (Table 1). However, there were 4 estimates of CCHD screening sensitivity that were based on exceptionally small numbers (≤10 total cases) and, for 3 of them, there was no sample variance associated with the estimate. For these variables, we used a uniform distribution based on the lower and upper 95% confidence limits of the Wilson score exact 95% confidence interval (CI) (Table 1). We then used a Monte Carlo simulation approach and drew 10,000 samples from the distributions of each of the variable estimates, as described above. For each simulation, to avoid negative values, simulated values were truncated with a lower bound at zero cases. We summarized the results of the 10,000 simulations using the mean and a 95% uncertainty interval (UI) defined by the 2.5th and 97.5th percentiles of the distribution of simulated values. Because we had created mutually exclusive CCHD categories throughout the analysis, for each simulation we calculated the sum of each variable of interest and summarized the results of the simulation using the same statistics (mean, 95% UI) to obtain our estimates for “all CCHDs.” To further reflect uncertainty in our estimates, we rounded estimates to the nearest 5 cases.

As a secondary analysis, we repeated the analysis under scenarios of “lower” and “higher” prevalence of prenatal diagnosis than the current estimates. Using NBDPS data, we identified the 3 sites with the highest and 3 with the lowest prevalence of prenatal detection. We calculated the prevalence of prenatal diagnosis and late detection within each of these subgroups and used them as separate inputs into our simulation model, while keeping the same estimates for birth prevalence and CCHD screening sensitivity as in the primary analysis. Analyses were performed by using SAS, version 9.3 (SAS Institute, Cary, NC). The MACDP was approved by the institutional review board at the Centers for Disease Control and Prevention and NBDPS by institutional review boards at the Centers for Disease Control and Prevention and study sites.
TABLE 1 Simulation Model Inputs Used To Estimate the Number of True-Positive and False-Negative Nonsyndromic CCHD Cases Resulting From CCHD Screening Using Pulse Oximetry in 2012 in the United States, Assuming Universal Implementation of CCHD Screening in All States

<table>
<thead>
<tr>
<th>CCHD Type (Nonsyndromic Cases Only)</th>
<th>Live-Birth Prevalence per 10 000 Births (SE)a</th>
<th>Prenatal Detection, % (SE)b</th>
<th>Late Detection, % (SE)c</th>
<th>Sensitivity of CCHD Screening Through Pulse Oximetry, % (SE)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary targets of CCHD screening</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLHS</td>
<td>1.66 (0.23)</td>
<td>56 (3.2)</td>
<td>30 (4.4)</td>
<td>91 (6.1)</td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>0.42 (0.12)</td>
<td>51 (5.8)</td>
<td>11 (5.1)</td>
<td>44–100a</td>
</tr>
<tr>
<td>TOF</td>
<td>3.90 (0.36)</td>
<td>26 (2.1)</td>
<td>36 (2.6)</td>
<td>39 (9.2)</td>
</tr>
<tr>
<td>TAPVR</td>
<td>0.55 (0.13)</td>
<td>5 (2.2)</td>
<td>39 (4.8)</td>
<td>91 (6.1)</td>
</tr>
<tr>
<td>d-TGA</td>
<td>2.17 (0.27)</td>
<td>28 (2.3)</td>
<td>19 (2.4)</td>
<td>92 (3.9)</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>0.45 (0.12)</td>
<td>45 (7.1)</td>
<td>19 (7.5)</td>
<td>44–97a</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>0.39 (0.11)</td>
<td>49 (8.4)</td>
<td>39 (11.5)</td>
<td>91 (8.7)</td>
</tr>
<tr>
<td>Secondary targets of CCHD screening</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COA or IAA</td>
<td>3.67 (0.34)</td>
<td>16 (1.5)</td>
<td>72 (2.2)</td>
<td>38 (6.8)</td>
</tr>
<tr>
<td>Double-outlet right ventricle</td>
<td>0.16 (0.07)</td>
<td>40 (6.4)</td>
<td>46 (8.4)</td>
<td>57–100a</td>
</tr>
<tr>
<td>Ebstein anomaly</td>
<td>0.62 (0.14)</td>
<td>19 (5.4)</td>
<td>23 (6.4)</td>
<td>48 (6.4)f</td>
</tr>
<tr>
<td>Single ventricle complex</td>
<td>0.75 (0.16)</td>
<td>55 (6.1)</td>
<td>37 (8.8)</td>
<td>61–100e</td>
</tr>
<tr>
<td>Multiple CCHDs</td>
<td>0.36 (0.11)</td>
<td>50 (4.9)</td>
<td>28 (5.9)</td>
<td>71 (3.2)f</td>
</tr>
<tr>
<td>All nonsyndromic CCHDs-e</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SEs were based on a normal distribution.

a Adapted from an analysis by Oster et al11 of CCHD live-birth prevalence from 2000 to 2005 using data from the MACDP.

b Adapted from an analysis by Ailes et al10 of the frequency of maternal report of prenatal CHD diagnosis from 2000 to 2005 and an analysis by Peterson et al8 of the prevalence of late CCHD detection by using data from the NBDPS; defined as the proportion of cases with either a maternal report of a prenatal diagnosis and/or a documented fetal echocardiography occurring before the date of birth.

c Adapted from an analysis by Peterson et al8 of the prevalence of late CCHD detection by using data from the NBDPS; defined as the number of cases not prenatally diagnosed that had a documented pediatric echocardiography occurring >3 days after birth.

d For all defects except for Ebstein anomaly and multiple CCHDs, this information was derived from the analysis by Prudhoe et al14 of the sensitivity of CCHD screening through pulse oximetry.

e The exact 95% CI was used when total was ≤10.

f Calculated as the average of the pulse oximetry sensitivities, among the secondary CCHD screening targets with sensitivities reported by Prudhoe et al14 (for Ebstein anomaly), or as the average of the pulse oximetry sensitivities, among all CCHD screening targets with sensitivities reported by Prudhoe et al14 (for multiple CCHDs).

g Adapted from an analysis by Peterson et al8 of the prevalence of late CCHD detection by using data from the NBDPS; de

RESULTS

As inputs for our simulation, we estimated that the 2000–2005 live-birth prevalence for specific nonsyndromic CCHDs ranged from 0.36 (0.11) per 10 000 births for multiple CCHDs to 3.90 (0.36) per 10 000 births for TOF (Table 1). Prenatal diagnosis was most frequent for HLHS and single ventricle and lowest for TAPVR and COA/IAA. Late detection (diagnosis at ≥3 days of birth) was more common for infants with COA/IAA and less frequent for infants with pulmonary atresia and d-TGA.

The simulation estimated that 5965 infants (95% UI: 5415–6515) are born alive with at least 1 nonsyndromic CCHD annually in the United States, with TOF, COA/IAA, d-TGA, and HLHS accounting for ≥75% of all live-born CCHD cases (Table 2). Excluding CCHD cases estimated to be detected prenatally (n = 1800 overall), an estimated 2410 CCHDs (95% UI: 2150–2680) would receive a timely diagnosis and 1755 CCHD cases (95% UI: 1540–1980) would be detected “late” (at >3 days of birth) and be most likely to benefit from CCHD screening through pulse oximetry; infants with COA/IAA accounted for approximately half of late-detected cases.

After accounting for the estimates of CCHD screening sensitivity using pulse oximetry, we estimated that 875 (95% UI: 705–1060) infants with CCHDs in the United States, including 470 (95% UI: 360–585) among primary CCHD screening targets alone, would be detected by using CCHD screening through pulse oximetry (true positives) each year, corresponding to ~15% of all CCHD cases (Fig 2). An additional 880 (95% UI: 700–1080; 280 [95% UI: 195–385] among primary screening targets alone) would be missed (false negatives), corresponding to ~15% of all CCHD cases (Fig 2). COA/IAA and TOF cases were the main contributors to both of these estimates.

CCHD screening through pulse oximetry appears to offer the greatest benefit for infants with TAPVR, double-outlet right ventricle, and COA/IAA; 20% to 30% of cases of each of these defects were estimated to be detected through CCHD screening with the use of pulse oximetry (Fig 2).

In our secondary analysis, under a scenario assuming “low” prenatal detection across the United States (19% across all CCHD types; Supplemental Table 4), we estimated that ~1105 (95% UI: 885–1350) true-positive and 1020 (95% UI: 805–1260) false-negative CCHD cases would result from CCHD screening by using pulse oximetry, corresponding to ~2.80 and 2.58 cases per 10 000 live births annually (Table 3). Comparatively, in a scenario assuming “high” prenatal detection (41% across all CCHD types; Supplemental Table 4), we estimated that ~740 (95% UI: 575–925) true-positive and
## TABLE 2 Monte Carlo Simulation Model Estimates of the Number of Nonsyndromic CCHD Cases in 2012 in the United States Estimated to be Born Alive, Prenatally Diagnosed, Born Undiagnosed, Timely Detected, and Late Detected and True Positives and False Negatives Resulting From CCHD Screening Through Pulse Oximetry Assuming Universal Implementation of CCHD Screening in All States

<table>
<thead>
<tr>
<th>CCHD Type</th>
<th>Estimated Number of CCHD Cases in 2012, Mean (95% UI)</th>
<th>True Positives</th>
<th>False Negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Born Alive</td>
<td>Prenatally Diagnosed</td>
<td>Born Undiagnosed</td>
<td>Timely Detected</td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>165 (75–255)</td>
<td>95 (40–140)</td>
<td>80 (35–135)</td>
</tr>
<tr>
<td>TOF</td>
<td>1540 (1285–1815)</td>
<td>845 (310–500)</td>
<td>1135 (620–1350)</td>
</tr>
<tr>
<td>TAPVR</td>
<td>220 (115–320)</td>
<td>10 (0–25)</td>
<td>205 (105–305)</td>
</tr>
<tr>
<td>d-TGA</td>
<td>890 (855–1065)</td>
<td>240 (175–315)</td>
<td>620 (465–775)</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>180 (85–275)</td>
<td>80 (35–135)</td>
<td>100 (45–160)</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>155 (70–240)</td>
<td>75 (30–130)</td>
<td>80 (35–135)</td>
</tr>
</tbody>
</table>

Secondary targets

| COA and IAA | 1450 (1185–1720) | 235 (175–300) | 2125 (890–1450) | 345 (265–435) | 870 (705–1050) |
| Double-outlet right ventricle | 65 (10–120) | 26 (5–90) | 40 (5–75) | 20 (5–45) | 20 (5–35) |
| Ebstein anomaly | 245 (135–350) | 45 (15–85) | 195 (105–290) | 150 (80–230) | 45 (20–35) |
| Single ventricle complex | 160 (690–240) | 135 (75–205) | 85 (40–140) | 50 (20–90) | 20 (5–40) |
| Subtotal | 2050 (1740–2370) | 465 (360–575) | 1585 (1325–1845) | 600 (480–730) | 985 (810–1165) |
| Multiple CCHDs | 140 (90–225) | 70 (30–120) | 70 (30–115) | 50 (20–85) | 20 (5–35) |
| All nonsyndromic CCHDs | 5985 (5145–6515) | 1800 (1580–2020) | 4185 (3785–4580) | 2410 (2150–2890) | 1755 (1540–1800) |

Results of Monte Carlo simulation using 10,000 iterations. The mean number born alive should equal the mean number prenatally diagnosed plus the mean number born undetected, and the mean number born undiagnosed should equal the mean number timely detected plus the mean number late detected, but any differences in the total are due to rounding all estimates to the nearest 5 cases.

a Calculated by using the number of live births in 2012 (3,952,597).b

We estimated that 900 infants with primary and secondary targets of CCHD screening with the use of pulse oximetry, corresponding to 1.99 cases per 10,000 live births annually (Table 3).
Our estimate of the number of infants with CCHDs likely to be detected through screening (875; 95% UI: 705–1060) is similar to the 1189 estimate from a recent cost-effectiveness analysis. Differences may be attributable to the inclusion of infants with genetic syndromes in the cost-effectiveness analysis or their use of overall estimates of prenatal diagnosis, late detection, and screening sensitivity for all CCHDs combined rather than each specific CCHD type. Our estimate differs from that suggested by a report describing the first 9 months of CCHD screening in New Jersey, the first state to mandate and implement statewide CCHD screening, which found that 3 infants with CCHDs were detected through screening alone. If extrapolated to the annual US birth population, the New Jersey experience equates to ~220 CCHD cases, which is much lower than our estimate. One potential reason for this discrepancy may be differences in prenatal diagnosis prevalence. Of the 55 infants with CCHDs identified in the New Jersey study, 48 (87%) were not reported as having a failed screen for a number of potential reasons, including having a prenatal diagnosis.

In our analysis, a large proportion of nonsyndromic CCHD cases estimated to be both missed and detected through CCHD screening were infants with COA/IAA. Because COA can have varying degrees of severity that may confer varying levels of hypoxia, it is possible that the more severe cases of coarctation are more likely to be detected prenatally or possibly identified through CCHD screening, but less severe cases may be missed. Furthermore, unlike some previous studies of CCHD screening sensitivity, our CCHD definition allowed for diagnosis of CCHD within 1 year, rather than 28 days, of life, also potentially leading us to include less severe cases of COA. However, we were unable to examine the impact of severity of these lesions on the likelihood of being detected prenatally or through CCHD screening.
because information on severity was not available in our data sources.

Although this analysis focused on CCHD cases likely to be detected and missed through universal CCHD screening, infants with non-CCHD conditions are likely to result in "false-positive" screens. In a meta-analysis of 13 studies of CCHD screening through pulse oximetry, Thangaratinam et al.\textsuperscript{13} estimated the false-positive rate to be 0.14% (95% CI: 0.06%–0.33%), which dropped to 0.05% (95% CI: 0.02%–0.12%) when screening was conducted at >24 hours after birth, the time frame recommended by the AAP, the AHA, and others.\textsuperscript{7} Although infants with false-positive screens do not have CCHDs, they may have other clinically relevant conditions that contributed to their failed screening, including pneumonia and sepsis.\textsuperscript{4,21}

Our analysis was subject to additional limitations. We restricted our estimates of birth prevalence, prenatal diagnosis, and late detection to 2000–2005 because we were only able to obtain maternal report of prenatal diagnosis through 2005 in the NBDPS.\textsuperscript{10} Our birth prevalence estimates were restricted to only the 5 central counties of metropolitan Atlanta and our prenatal diagnosis and late detection estimates were derived from a study conducted in 10 states; thus, our estimates may not be reflective of the entire United States. Despite potential improvements in prenatal diagnosis over time\textsuperscript{22} and differing definitions of prenatal diagnosis, our range of prenatal diagnosis estimates from 2000–2005 NBDPS data was consistent with those from a study that used national 2006–2012 Society of Thoracic Surgeons data (unpublished data), and our "high" prenatal diagnosis estimates were similar to a recent analysis of Massachusetts data.\textsuperscript{22} Our definition of late-detected CCHDs was based on the timing of the first-documented echocardiography confirming the defect, not necessarily

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Estimated Number of CCHD Cases in 2012a</th>
<th>Prevalence</th>
<th>Detection</th>
<th>True Positives</th>
<th>False Negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Born Alive</td>
<td>N Per 10,000 Births</td>
<td>n, Mean (95% UI) % Per 10,000 Births</td>
<td>n, Mean (95% UI) % Per 10,000 Births</td>
<td>n, Mean (95% UI) % Per 10,000 Births</td>
<td>n, Mean (95% UI) % Per 10,000 Births</td>
</tr>
<tr>
<td>Primary</td>
<td>5585</td>
<td>51.09 (45.00–60.00)</td>
<td>17</td>
<td>4.35 (3.50–5.20)</td>
<td>24</td>
</tr>
<tr>
<td>Low</td>
<td>5970</td>
<td>15.10 (12.00–17.30)</td>
<td>11</td>
<td>2.77 (2.20–3.40)</td>
<td>16</td>
</tr>
<tr>
<td>High</td>
<td>5985</td>
<td>15.09 (12.00–17.30)</td>
<td>24</td>
<td>5.12 (4.30–6.00)</td>
<td>46</td>
</tr>
</tbody>
</table>

Results of Monte Carlo simulation using 10,000 iterations. Differences in the number born alive are due to rounding. Birth prevalence estimates were restricted to only the 5 central counties of metropolitan Atlanta and our prenatal diagnosis and late detection estimates were derived from a study conducted in 10 states; thus, our estimates may not be reflective of the entire United States. Despite potential improvements in prenatal diagnosis over time\textsuperscript{22} and differing definitions of prenatal diagnosis, our range of prenatal diagnosis estimates from 2000–2005 NBDPS data was consistent with those from a study that used national 2006–2012 Society of Thoracic Surgeons data (unpublished data), and our "high" prenatal diagnosis estimates were similar to a recent analysis of Massachusetts data.\textsuperscript{22} Our definition of late-detected CCHDs was based on the timing of the first-documented echocardiography confirming the defect, not necessarily
the first time echocardiography was ever performed; thus, some infants may have been misclassified. However, our overall estimate of late detection is similar to that of a study in a cohort of Florida births, in which the authors defined late detection as diagnosis after birth hospitalization. In addition, it is possible that some infants that we classified as having “timely” diagnosis could still have benefited from screening; thus, our estimates may be altered if screening is performed earlier. An additional limitation is that we relied on published estimates of CCHD-specific screening sensitivity that included studies with screening algorithms different from that recommended by the AAP, AHA, and others and we were unable to assess the impact of these differences, such as the age at screening, in our study. It is possible that the classification of specific defects differed across our other data sources (MACDP, NBDPS, Prudhoe et al). Finally, our estimates of the number of infants potentially detected through CCHD screening only apply to the subset of infants, estimated to be ~88%, with CCHDs not associated with a genetic syndrome.

In the absence of national implementation and data collection on CCHD screening, our analysis used modeling approaches to estimate the potential impact of screening and had several strengths, which make it a valuable contribution to the literature. We used data from a population-based active surveillance system to estimate CCHD prevalence and a population-based case-control study to estimate prenatal diagnosis and late detection. To better account for uncertainty, we used a range of estimates for our model variables (typically the mean and SE). In addition, estimates from our secondary analysis allow public health professionals and policy makers to consider the prevalence of prenatal diagnosis in their communities when estimating the likely impact of CCHD screening.

CONCLUSIONS

On the basis of our model, nearly 900 infants per year with nonsyndromic CCHDs are likely to be detected through universal CCHD screening in the United States; however, an equal number are likely to be missed. Although many infants with CCHDs will likely be identified through screening, there will still be many false negatives, suggesting that the general practitioner should not rely on CCHD screening alone to rule out a CCHD. Our analysis also suggests that increases in prenatal diagnosis of CCHDs are unlikely to substantially impact the number of infants detected through CCHD screening. Future efforts should focus on documenting the true impact of CCHD screening in practice, and linking CCHD screening data with birth defects surveillance data, to identify the outcome of infants with false-negative screening results.

* Calculation: 3 infants identified in 9 months is equivalent to 4 infants identified in 12 months; 4 infants identified through screening per 73,000 births in New Jersey × ~4,000,000 births in the United States = 219/year in the United States.

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Pediatrics 2015;135;1000; originally published online May 11, 2015; DOI: 10.1542/peds.2014-3662

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Estimated Number of Infants Detected and Missed by Critical Congenital Heart Defect Screening
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*Pediatrics* 2015;135;1000; originally published online May 11, 2015;
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