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

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Abstract

Background and objectives—In 2011, the U.S. Secretary of Health and Human Services recommended universal screening of newborns for critical congenital heart defects (CCHD), yet few estimates of the number of infants with CCHD likely to be detected through universal screening exist. Our objective was to estimate the number of infants with nonsyndromic CCHD in the United States likely to be detected (true positives) and missed (false negatives) through 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 seven primary and five secondary targets of CCHD screening identified through screening.

Results—We estimated that 875 (95% uncertainty interval [UI]: 705–1,060) U.S. infants with nonsyndromic CCHD, including 470 (95% UI: 360–585) among primary CCHD screening targets, will be detected annually through CCHD newborn screening. An additional 880 (UI: 700–1,080) false negative screenings, including 280 (95% UI: 195–385) among primary screening targets, are expected. We estimated that similar numbers of CCHD (within ~1 case/10,000 live births) would

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Contributor's Statement Page

Elizabeth C. Ailes: Dr. Ailes conceptualized and designed the study, acquired the data, carried out the analysis and interpretation of the data, drafted the initial manuscript, reviewed and revised the manuscript, approved the final manuscript as submitted, and agrees 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.

Suzanne M. Gilboa, Margaret A. Honein, and Matthew E. Oster: Drs. Gilboa, Honein, and Oster conceptualized and designed the study, reviewed and revised the manuscript, 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.

¹Calculation: three infants identified in nine months is equivalent to four infants identified in 12 months; 4 infants identified through screening/73,000 births in New Jersey x ~ 4,000,000 births in the U.S. = 219/year in the U.S.

be detected under scenarios comparing “lower” (~19%) and “higher” (~42%) 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.

Keywords

heart defects; congenital; neonatal screening; Monte Carlo methods

INTRODUCTION

Congenital heart defects (CHD) affect ~8/1,000 births and ~25% are considered critical congenital heart defects (CCHD).¹ In 2011 the U.S. Secretary of Health and Human Services recommended adding CCHD to the newborn Recommended Uniform Screening Panel.² Subsequently, screening for CCHD through pulse oximetry, used to supplement standard clinical evaluation and monitoring of newborns, has been implemented in many hospitals.^{3–5} Screening protocols vary regarding the age of the newborn at screening and the use of pre- and/or post-ductal oxygen saturation measurements.^{4,6} The American Academy of Pediatrics (AAP), American Heart Association (AHA), and others recommend screening infants at 24–48 hours of life with consideration of both pre- and post-ductal measurements.⁷

Estimates of the impact of CCHD screening differ.^{4,8,9} Differences in prenatal diagnosis and “late” detection (i.e., CCHD diagnosis after birth hospital discharge⁹ or after three days of life⁸) by CCHD type and geographic location might contribute to the observed variation.^{8,10–12} Another potential contributor is the sensitivity of the pulse oximetry screening test; although the overall sensitivity is estimated to be 76%,¹³ it varies considerably by CCHD type, ranging from 36–100%.¹⁴

Estimating the number of infants potentially detected (“true positives”) and missed (“false negatives”) through universal CCHD screening must incorporate three 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 occur through CCHD screening using pulse oximetry.

PATIENTS AND METHODS

We included the seven CCHD 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).⁷ We also included the five “secondary” targets of CCHD screening: coarctation of the aorta (COA), double-outlet right ventricle (DORV), Ebstein anomaly, interrupted aortic arch (IAA), and single ventricle.¹ While critical aortic

and pulmonary stenoses are also typically considered CCHD, we lacked complete data on lesion severity.¹⁵ We combined COA and IAA into one category (COA/IAA) as this was done for one of our data sources.¹⁴ To calculate estimates for “all CCHD” by summing across the specific CCHD estimates, we created a “multiple CCHD” category including those cases with multiple CCHD diagnoses, such that no case was counted more than once. We restricted the analysis to infants with CCHD diagnosed before 1 year of life. To better reflect the population of infants eligible for CCHD screening, all analyses were restricted to liveborn 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 CCHD using data from the Metropolitan Atlanta Congenital Defects Program (MACDP), an active surveillance system for major birth defects in metropolitan Atlanta, Georgia.¹⁶ Surveillance is conducted for infants, fetuses, and stillbirths >20 weeks gestation with major birth defects identified before six 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.¹⁷ For our analysis, we updated Oster et al.’s (2013)¹⁵ analysis to calculate the 2000–2005 live birth prevalence of the 12 selected CCHD types.

Frequency of Prenatal Diagnosis

Prenatal diagnosis was estimated using data from the National Birth Defects Prevention Study (NBDPS), a multisite case-control study of risk factors for select major birth defects, including CCHD.¹⁸ Cases were identified through birth defects surveillance systems in ten U.S. sites; infants with recognized or strongly suspected single gene disorders or chromosomal abnormalities were excluded. Trained abstractors reviewed medical records of infants/fetuses with CCHD and, to be included in the study, CCHD cases had to be confirmed by echocardiography, cardiac catheterization, surgery, or autopsy.¹⁸ Prenatally diagnosed cases were only included if confirmed by autopsy or by a clinician with expertise in pediatric cardiology.¹⁹ CCHD type(s) were assigned by physicians with specialized training in clinical genetics or pediatric cardiology.¹⁹ We defined prenatal diagnosis as either: 1) a maternal report of a prenatal diagnosis of a CHD (as had been done in a previous analysis¹⁰) 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.⁸ Previously, we categorized infants with echocardiography or autopsy information as having “timely” CCHD detection if their first documented echocardiography was within three days of birth and as having “late” CCHD detection if their first echocardiography (or autopsy) occurred after the third day of life.⁸ 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 CCHD”.¹⁴ 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 CCHD, to obtain an estimate for multiple CCHD.

Analysis

For each CCHD, we estimated the number of true positive and false negative cases resulting from CCHD screening through pulse oximetry (Figure 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 standard errors for these parameters (Table 1). However, there were four estimates of CCHD screening sensitivity that were based on exceptionally small numbers (≤ 10 total cases) and, for three of them, there was no sample variance associated with the estimate. For these parameters, we used a uniform distribution based on the lower and upper 95% confidence limits of the Wilson Score exact 95% confidence interval (Table 1). We then used a Monte Carlo simulation approach and drew 10,000 samples from the distributions of each of the parameter 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 parameter of interest and summarized the results of the simulation using the same statistics (mean, 95% UI) to obtain our estimates for “all CCHD”. To further reflect uncertainty in our estimates, we rounded estimates to the nearest five 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 three sites with the highest and three with the lowest prevalence of prenatal diagnosis. We calculated the prevalence of prenatal diagnosis and late detection within each of these sub-groups 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 using SAS, v.9.3 (SAS Institute, Cary, NC). MACDP was approved by the Institutional Review Board (IRB) at the Center for Disease Control and Prevention (CDC) and NBDPS by IRBs at the CDC and study sites.

RESULTS

As inputs for our simulation, we estimated that the 2000–2005 live birth prevalence for specific nonsyndromic CCHD ranged from 0.36 (0.11) per 10,000 births for multiple CCHD 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 5,965 infants (95% UI: 5,415–6,515) are born alive with at least one nonsyndromic CCHD annually in the United States, with TOF, COA/IAA, d-TGA and HLHS accounting for ~75% of all liveborn CCHD cases (Table 2). Excluding CCHD cases estimated to be detected prenatally (n=1,800 overall), an estimated 2,410 CCHD (95% UI: 2,150–2,680) would receive a timely diagnosis and 1,755 CCHD cases (95% UI: 1,540–1,980) 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: 705–1,060) infants with CCHD in the U.S., including 470 (95% UI: 360–585) among primary CCHD screening targets alone, would be detected using CCHD screening through pulse oximetry (true positives) each year, corresponding to about 15% of all CCHD cases (Figure 2). An additional 880 (95% UI: 700–1,080; 280 [95% UI: 195–385] among primary screening targets alone) would be missed (false negatives), corresponding to about 15% of all CCHD cases (Figure 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, DORV, and COA/IAA; 20–30% of cases of each of these defects were estimated to be detected through CCHD screening using pulse oximetry (Figure 2).

In our secondary analysis, under a scenario assuming “low” prenatal detection across the United States (19% across all CCHD types; eTable), we estimated that approximately 1,105 (95% UI: 885–1,350) true positive and 1,020 (95% UI: 805–1,260) false negative CCHD cases would result from CCHD screening using pulse oximetry, corresponding to approximately 2.80 and 2.58 cases per 10,000 live births annually (Table 3). Comparatively, in a scenario assuming “high” prenatal detection (42% across all CCHD types; eTable), we estimated that approximately 740 (95% UI: 575–925) true positive and an additional 785 (95% UI: 610–975) false negative CCHD cases would result from CCHD screening using pulse oximetry, corresponding to approximately 1.87 and 1.99 cases per 10,000 live births annually (Table 3).

DISCUSSION

We estimated that ~900 infants with nonsyndromic CCHD could be detected annually in the United States through universal implementation of CCHD screening using pulse oximetry. The majority of these infants would be those with CCHD less likely to be detected

positive” screens. In a meta-analysis of 13 studies of CCHD screening through pulse oximetry, Thangaratinam et al. (2012) 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 timeframe recommended by the AAP, AHA, and others.^{7,13} While infants with false positive screens do not have CCHD, they may have other clinically relevant conditions that contributed to their failed screening, including pneumonia and sepsis.^{4,21}

Our analysis was subject to additional limitations. We restricted our estimates of birth prevalence, prenatal diagnosis, and late detection to 2000–2005 as we were only able to obtain maternal report of prenatal diagnosis through 2005 in the NBDPS.¹⁰ Our birth prevalence estimates were restricted to only the five 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 time²² and differing definitions of prenatal diagnosis, our range of prenatal diagnosis estimates from 2000–2005 NBDPS data were consistent with those from a study using national 2006–2012 Society of Thoracic Surgeons data²³, and our “high” prenatal diagnosis estimates were similar to a recent analysis of Massachusetts data.²² Our definition of late detected CCHD 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 of a cohort of Florida births, in which the authors defined late detection as diagnosis after birth hospitalization.⁹ Additionally, 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 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 approximately 88%,¹⁵ with CCHD 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 making 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 parameters (typically the mean and standard error). Additionally, 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

Based on our model, nearly 900 infants per year with nonsyndromic CCHD are likely to be detected through universal CCHD screening in the United States; however, an equal number are likely to be missed. While many infants with CCHD 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.²⁵ Our analysis also suggests that increases in prenatal diagnosis of CCHD 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,²⁴ in order to identify the outcome of infants with false negative screening results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AAP	American Academy of Pediatrics
AHA	American Heart Association
COA	coarctation of the aorta
CCHD	critical congenital heart defects
d-TGA	dextro-transposition of the great arteries

DORV	double-outlet right ventricle
HLHS	hypoplastic left heart syndrome
IAA	interrupted aortic arch
MACDP	Metropolitan Atlanta Congenital Defects Program
NBDPS	National Birth Defects Prevention Study
TOF	tetralogy of Fallot
TAPVR	total anomalous pulmonary venous return
UI	uncertainty interval

What's Known on This Subject

Newborn screening for critical congenital heart defects (CCHD) has been implemented in many hospitals, yet there is uncertainty about the number of infants with CCHD 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 CCHD 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.

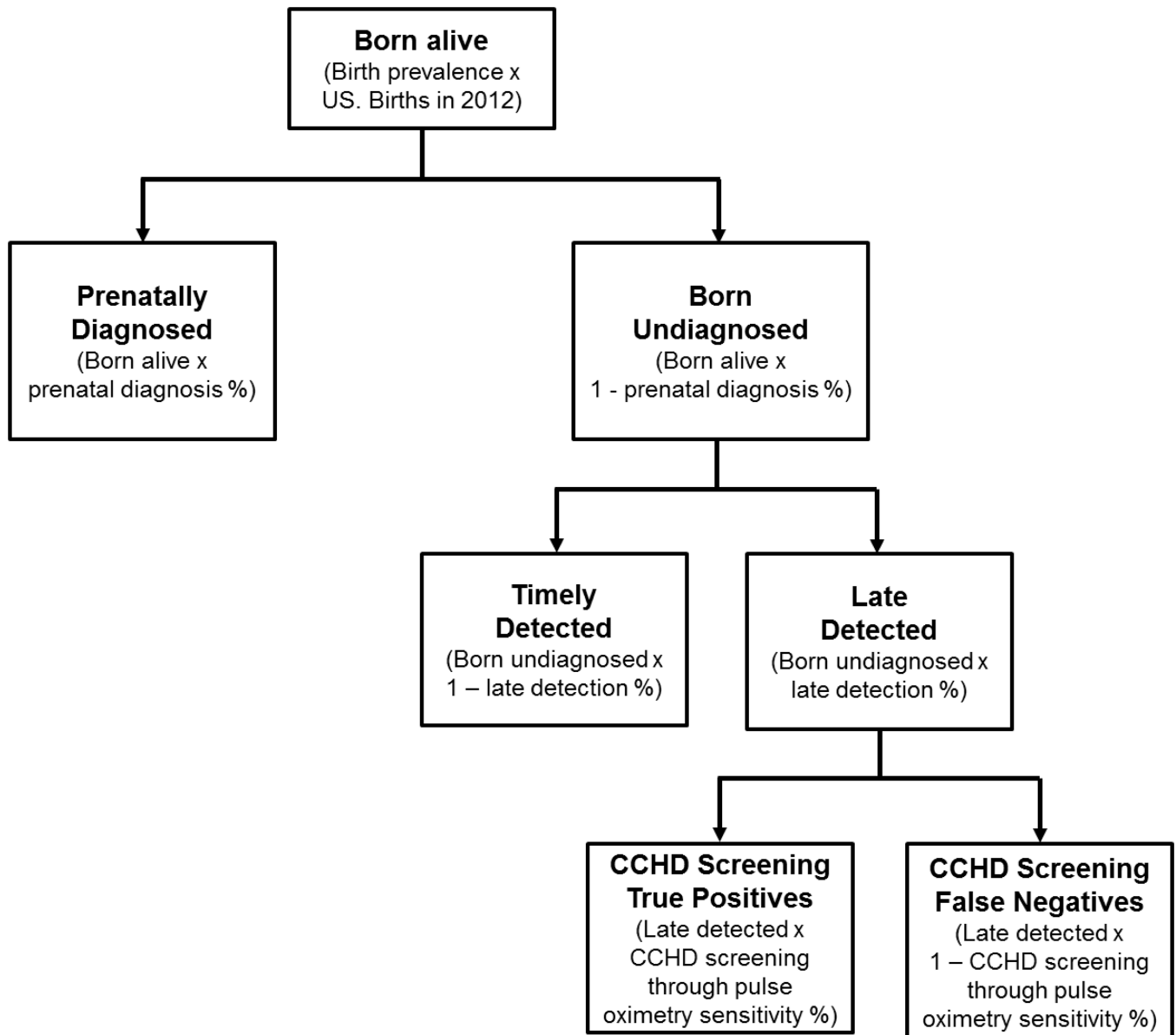


Figure 1.

Model estimating the number of U.S. nonsyndromic critical congenital heart defect (CCHD) cases in 2012 estimated to be born alive, prenatally diagnosed, born undiagnosed, timely detected, late detected, and false negatives and true positives of CCHD screening through pulse oximetry, assuming universal implementation of CCHD screening in all states

Notes: CCHD=critical congenital heart defects

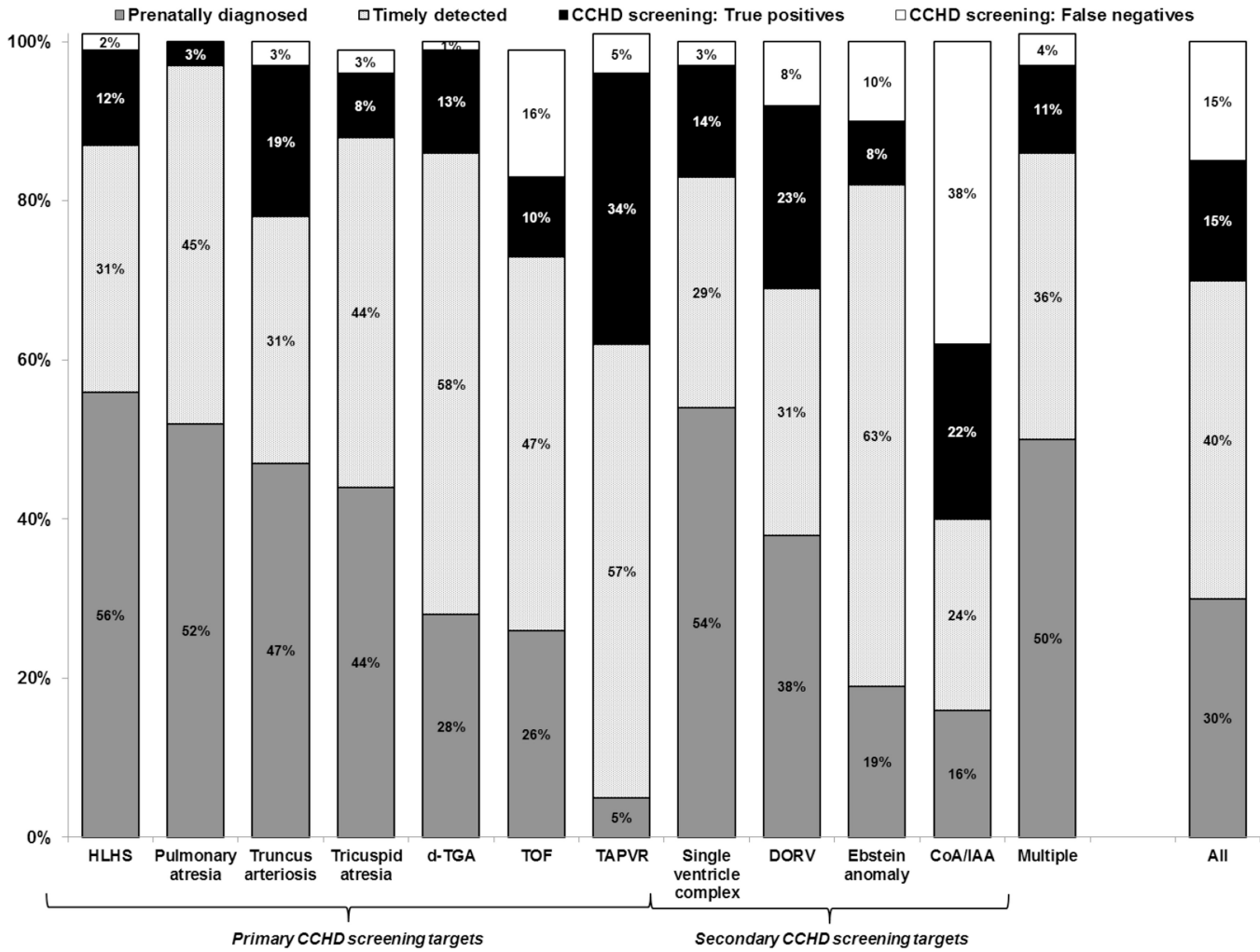


Figure 2. Proportion of U.S. nonsyndromic critical congenital heart defect (CCHD) cases in 2012 estimated to be prenatally diagnosed, timely detected, and true positive, and false negative of CCHD screening through pulse oximetry, by CCHD type, assuming universal implementation of CCHD screening in all states
 Notes: CCHD=critical congenital heart defects; HLHS=hypoplastic left heart syndrome; d-TGA=dextro-transposition of the great arteries; TOF=tetralogy of Fallot; TAPVR=total anomalous pulmonary venous return; DORV=double outlet right ventricle; COA/IAA=coarctation of the aorta/interrupted aortic arch; Multiple=Multiple critical congenital heart defects

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Simulation model inputs used to estimate the number of true positive and false negative nonsyndromic critical congenital heart defect (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 1

CCHD type (nonsyndromic cases only)	Live birth prevalence per 10,000 births (SE) ^a	Prenatal detection (SE) ^b	Late detection (SE) ^c	Sensitivity of CCHD screening through pulse oximetry (SE) ^d
Primary targets of CCHD screening				
Hypoplastic left heart syndrome	1.66 (0.23)	56% (3.2%)	30% (4.4%)	91% (6.1%)
Pulmonary atresia	0.42 (0.12)	51% (5.8%)	11% (5.1%)	44%–100% ^e
Tetralogy of Fallot	3.90 (0.36)	26% (2.1%)	36% (2.6%)	39% (9.2%)
Total anomalous pulmonary venous return	0.55 (0.13)	5% (2.2%)	39% (4.8%)	91% (6.1%)
Dextro-transposition of the great arteries	2.17 (0.27)	28% (2.3%)	19% (2.4%)	92% (3.9%)
Tricuspid atresia	0.45 (0.12)	45% (7.1%)	19% (7.5%)	44%–97% ^e
Truncus arteriosus	0.39 (0.11)	49% (8.4%)	39% (11.5%)	91% (8.7%)
Secondary targets of CCHD screening				
Coarctation of the aorta or interrupted aortic arch	3.67 (0.34)	16% (1.6%)	72% (2.2%)	36% (6.8%)
Double outlet right ventricle	0.16 (0.07)	40% (6.4%)	46% (8.4%)	57%–100% ^e
Ebstein anomaly	0.62 (0.14)	19% (5.4%)	23% (6.4%)	48% (6.4%) ^f
Single ventricle complex	0.75 (0.16)	55% (6.1%)	37% (8.8%)	61%–100% ^e
Multiple CCHD	0.36 (0.11)	50% (4.6%)	28% (5.9%)	71% (3.2%) ^f
All nonsyndromic CCHDs^g	-	-	-	-

Notes. SE=standard error based on a normal distribution

^a Adapted from an analysis by Oster et al. (2013)¹⁵ of CCHD live birth prevalence from 2000–2005 using data from the Metropolitan Atlanta Congenital Defects Program

^b Adapted from an analysis by Ailes et al. (2013)¹⁰ of the frequency of maternal report of prenatal congenital heart defects diagnosis from 2000–2005 and an analysis by Peterson et al. (2014)⁸ of the prevalence of late CCHD detection using data from the National Birth Defects Prevention Study (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 al. (2014)⁸ of the prevalence of late CCHD detection using data from the NBDPS; defined as the number of cases not prenatally diagnosed that had a documented pediatric echocardiography occurring more than three days after birth

^d For all defects except Ebstein anomaly and multiple CCHD, this information was derived from the analysis by Prudhoe et al. (2013)¹⁴ of the sensitivity of CCHD screening through pulse oximetry

^e Exact 95% confidence interval 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 al. (2013) (for Ebstein anomaly) or as the average of the pulse oximetry sensitivities, among all CCHD screening targets with sensitivities reported by Prudhoe et al. (2013) (for multiple CCHD)

^g No model inputs were used for the “all nonsyndromic CCHD” category as estimates of the number of cases detected/missed through CCHD screening through pulse oximetry were derived by summing across the CCHD categories for each of the 10,000 simulations, then calculating the mean, median and 95% uncertainty interval across the 10,000 simulations for a given parameter

Monte Carlo simulation model estimates of the number of nonsyndromic critical congenital heart defect (CCHD) cases in 2012 in the United States estimated to be born alive, prenatally diagnosed, born undiagnosed, timely detected, 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 2

CCHD type	Results of Monte Carlo simulation using 10,000 iterations							CCHD screening through pulse oximetry	
	Born alive	Prenatally diagnosed	Born undiagnosed	Timely detected	Late detected	True positives	False negatives	True positives	False negatives
Primary targets									
Hypoplastic left heart syndrome	655 (475–835)	365 (260–475)	290 (200–380)	200 (135–275)	85 (55–125)	80 (50–120)	10 (0–20)	80 (50–120)	10 (0–20)
Pulmonary atresia	165 (75–255)	85 (40–140)	80 (35–135)	75 (30–120)	10 (0–20)	5 (0–15)	0 (0–10)	5 (0–15)	0 (0–10)
Tetralogy of Fallot	1,540 (1,265–1,815)	405 (310–500)	1,135 (920–1,350)	730 (580–885)	405 (315–505)	160 (80–250)	245 (160–345)	160 (80–250)	245 (160–345)
Total anomalous pulmonary venous return	220 (115–320)	10 (0–25)	205 (105–305)	125 (65–190)	80 (40–125)	75 (35–115)	10 (0–20)	75 (35–115)	10 (0–20)
Dextro-transposition of the great arteries	860 (655–1,065)	240 (175–315)	620 (465–775)	500 (375–630)	120 (80–160)	110 (70–150)	10 (0–20)	110 (70–150)	10 (0–20)
Tricuspid atresia	180 (85–275)	80 (35–135)	100 (45–160)	80 (35–135)	20 (5–40)	15 (0–35)	5 (0–10)	15 (0–35)	5 (0–10)
Truncus arteriosus	155 (70–240)	75 (30–130)	80 (35–135)	50 (20–90)	30 (10–65)	30 (10–60)	5 (0–10)	30 (10–60)	5 (0–10)
Subtotal	3,770 (3,345–4,190)	1,260 (1,085–1,445)	2,510 (2,200–2,815)	1,760 (1,535–1,995)	750 (630–880)	470 (360–585)	280 (195–385)	470 (360–585)	280 (195–385)
Secondary targets									
Coarctation of the aorta and interrupted aortic arch	1,450 (1,185–1,720)	235 (175–300)	1215 (990–1450)	345 (265–435)	870 (705–1050)	315 (190–455)	560 (410–730)	315 (190–455)	560 (410–730)
Double outlet right ventricle	65 (10–120)	25 (5–50)	40 (5–75)	20 (5–45)	20 (0–35)	15 (0–30)	5 (0–10)	15 (0–30)	5 (0–10)
Ebstein anomaly	245 (135–350)	45 (15–85)	195 (105–290)	150 (80–230)	45 (20–85)	20 (10–40)	25 (10–45)	20 (10–40)	25 (10–45)
Single ventricle complex	295 (175–415)	160 (90–240)	135 (75–205)	85 (40–140)	50 (20–85)	40 (15–75)	10 (0–25)	40 (15–75)	10 (0–25)
Subtotal	2,050 (1,740–2,370)	465 (360–575)	1,585 (1,325–1,845)	600 (480–730)	985 (810–1,165)	390 (260–535)	595 (445–765)	390 (260–535)	595 (445–765)
Multiple CCHD	140 (60–225)	70 (30–120)	70 (30–115)	50 (20–85)	20 (5–35)	15 (5–25)	5 (0–10)	15 (5–25)	5 (0–10)

Results of Monte Carlo simulation using 10,000 iterations

Mean (95% uncertainty interval) of the estimated number of CCHD cases in 2012^a that would be...

CCHD type	Born alive	Prenatally diagnosed	Born undiagnosed	Timely detected	Late detected	CCHD screening through pulse oximetry	
						True positives	False negatives
All nonsyndromic CCHD^b	5,965 (5,415–6,515)	1,800 (1,580–2,020)	4,165 (3,765–4,580)	2,410 (2,150–2,680)	1,755 (1,540–1,980)	875 (705–1,060)	880 (700–1,080)

Notes: 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 five cases

^a Calculated using the number of live births in 2012 (3,952,937)²⁶

^b No model inputs were used for the “all nonsyndromic CCHD” category as estimates of the number of cases detected/missed through CCHD screening through pulse oximetry were derived by summing across the CCHD categories for each of the 10,000 simulations, then calculating the mean, median and 95% uncertainty interval across the 10,000 simulations for a given parameter

Table 3

Monte Carlo simulation model estimates of number of nonsyndromic critical congenital heart defect (CCHD) cases in 2012 in the United States estimated to be prenatally diagnosed, timely detected, and true positives and false negatives resulting from CCHD screening through pulse oximetry, assuming universal implementation of CCHD screening in all states, in the primary analysis and under scenarios of low and high prenatal diagnosis prevalence

Results of Monte Carlo simulation using 10,000 iterations														
Mean (95% uncertainty interval) of the estimated number of CCHD cases in 2012 ^{a,b} that would be...														
Born alive			Prenatally diagnosed			Timely detected			CCHD screening through pulse oximetry					
									True positives			False negatives		
Analysis	N	Per 10,000 births	N	(%)	Per 10,000 births	N	(%)	Per 10,000 births	N	(%)	Per 10,000 births	N	(%)	Per 10,000 births
Primary	5,965	15.09	1,800 (1,580–2,020)	(30%)	4.55	2,410 (2,150–2,680)	(40%)	6.10	875 (705–1,060)	(15%)	2.21	880 (700–1,080)	(15%)	2.23
If prenatal diagnosis were universally...														
"Low" (~19%) ^c	5,970	15.10	1,095 (895–1,310)	(18%)	2.77	2,750 (2,415–3,100)	(46%)	6.96	1,105 (885–1,350)	(19%)	2.80	1,020 (805–1,260)	(17%)	2.58
"High" (~42%) ^c	5,965	15.09	2,455 (2,155–2,785)	(41%)	6.21	1,985 (1,720–2,270)	(33%)	5.02	740 (575–925)	(12%)	1.87	785 (610–975)	(13%)	1.99

Notes: Differences in the number born alive are due to rounding

^a Calculated using the number of live births in 2012 (3,952,937)²⁶

^b Model inputs were for each specific CCHD type and these estimates for all CCHD combined were derived by summing across the CCHD categories for each of the 10,000 simulations, then calculating the mean and 95% uncertainty interval across the 10,000 simulations for a given parameter

^c See Methods and eTable