

# Children with hemodynamically significant congenital heart disease can be identified through population-based registers

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**Background:** Epidemiological research is facilitated in Sweden by a history of national health care registers, making large unselected national cohort studies possible. However, for complex clinical populations, such as children with congenital heart disease (CHD), register-based studies are challenged by registration limitations. For example, the diagnostic code system *International Classification of Diseases*, 10th version (ICD-10) does not indicate the clinical significance of abnormalities, therefore may be of limited use if used as the sole parameter in epidemiological research. Palivizumab is indicated as a prophylactic treatment against respiratory syncytial virus infections in children with hemodynamically significant CHD.

**Aim:** The aim of the study reported here was to develop and validate an algorithm to identify children with hemodynamically significant CHD according to recommendations for palivizumab prophylaxis in register-based research.

**Methods:** By using a strategy of combining criteria for age at diagnosis, diagnostic codes, surgical procedure codes, and dispensing records, we created an algorithm to define the specific cases with hemodynamically significant CHD in which palivizumab could be advocated according to recommendations.

**Results:** The algorithm identified 928 children with hemodynamically significant CHD in the Swedish birth cohort born July 1, 2005 to December 31, 2010. A sensitivity (95% confidence interval) of 80% (70–88) for the algorithm was found by analyzing 121 children identified through local hospital data who were treated with palivizumab within a defined region and study period. The positive predictive value was estimated by medical record review in a random sample of 34 cases identified by the algorithm. In 79% (62–91) of these cases, the children were regarded as having hemodynamically significant CHD according to the recommendations for treatment with palivizumab.

**Conclusion:** It was possible to identify a subgroup of children with hemodynamically significant CHD using an epidemiological approach and an algorithm with high validity. Our results will enable well-powered national cohort studies of individuals with complex clinical conditions such as hemodynamically significant CHD.

**Keywords:** epidemiology, population-based registries, algorithm, national cohort studies, complex clinical conditions, palivizumab

## Introduction

The Nordic countries have a long tradition of register-based research. The research has been facilitated by national health care registers. The tracking of individual disease and prescription-drug-dispensing data over time is made feasible by linking individual information by the central personal registration (CPR) number, making large unselected national cohort studies possible.<sup>1,2</sup>

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For congenital heart disease (CHD), the diagnostic code system *International Classification of Diseases*, 10th version (ICD-10) presents challenges in the process of identifying a specific study population in register-based research. An ICD-10 code will mostly not differentiate between severe and mild disease. For example, the ICD-10 code Q21.0, for ventricular septal defect, does not differentiate between patients with a spontaneous closure of the defect and those with a hemodynamically significant disease with subsequent need of pharmacological and/or surgical treatment. As the diagnostic codes do not indicate the clinical importance of certain abnormalities, they may be of limited use in epidemiological research. Given these premises, the definition of a specific study population of children with hemodynamically significant CHD needs to be based on the combination of data regarding age at diagnosis, time course of the disease, ICD-10 codes, surgical procedures, and dispensing records of prescribed drugs.

Young children with hemodynamically significant CHD are at risk for respiratory syncytial virus infection, and palivizumab prophylaxis in these children reduces hospitalization.<sup>3</sup> “Palivizumab” is a monoclonal antibody administered as monthly injections during the respiratory syncytial virus infection season (October to April in the northern hemisphere). We undertook this study to assess whether the registers can be used to identify children with hemodynamically significant CHD in line with palivizumab recommendations. The aims were to develop and validate an algorithm to define hemodynamically significant CHD in children according to recommendations for palivizumab prophylaxis that can be used in future register-based research.

## Materials and methods

### Data and design

We conducted a national population-based register study including all children born July 1, 2005–December 31, 2010 in Sweden. Individuals’ unique CPR number was used to link information in the different national registries. For the study objective, to create an algorithm to identify a cohort of children with CHD, we obtained information on all diagnostic codes and surgical procedures from the National Patient Register.<sup>4</sup> Data on all dispensed prescribed medication were obtained from the Prescribed Drug Register.<sup>5</sup>

We aimed to define and subdivide cases with hemodynamically significant CHD in which palivizumab could be advocated (see clinical recommendations in Table 1). Hence, we used a strategy of combining criteria for age at diagnosis, diagnostic codes, surgical procedure codes, and dispensing records

**Table 1** The Medical Products Agency: Swedish recommendations for the treatment of children with hemodynamically significant congenital heart disease with palivizumab

Target group	Recommendation
1	Children below 6 months of age with a significant heart disease and Down syndrome or other chromosomal abnormality or known immunodeficiency or significant syndrome
2	Children below 6 months of age with left-to-right shunt
3	Children below 12 months of age with a univentricular heart or children where the primary pulmonary blood supply comes from a Glenn anastomosis
4	Children below 12 months of age with structural heart disease plus lung disease where surgical repair of the heart repair is performed before 1 year of age
5	Children below 12 months of age with idiopathic pulmonary hypertension or with pulmonary hypertension despite former heart surgery
6	Children below 12 months of age with a diagnosis of cardiomyopathy and heart failure who are on triple medication or have had a heart transplant before the age of 2 years

for prescribed drugs from the national registries. A condensed description of the algorithm is given in Table 2.

### Validation

The validity of the proposed algorithm with regard to an estimation of sensitivity and positive predictive value (PPV) was assessed in two steps.

### Sensitivity

Local and prospectively recorded data, including CPR numbers, on all children with heart disease treated with palivizumab were retrieved from two Swedish university hospitals (the Department of Pediatric Cardiology, Astrid Lindgren Children’s Hospital, Karolinska University Hospital, Stockholm, and the Department of Pediatric Cardiology, Uppsala University Hospital, Uppsala). During the recruitment period, 174,887 children were born in Stockholm or Uppsala out of 600,750 (29%) births in Sweden.<sup>6</sup> The results generated by the algorithm for all children born during the recruitment period were saved and matched against the selected children known from local hospital data to be treated with palivizumab.

In false-negative cases where the algorithm failed to identify a child, medical records were studied for diagnosis; time course; and pharmacological, surgical, or catheter interventional treatment. The data resulting from this medical record review were compared with the recommendations for treatment with palivizumab for estimation of the sensitivity.

**Table 2** Condensed description of algorithm\*

Interpretation group	Inclusion diagnosis	Inclusion procedure	Inclusion drugs	Exclusion criteria/on	Age restriction (months)
1	Q86, Q87, Q89, Q9, D80, D81, D82				
2	Q210 Q211 Q212 Q214 Q250	FHB, FHC, FBC FFC FHD, FFD, FBC FDD10, FDD13, FDD20 FDE	C03, C09	Surgery <1 month	<6
3	Q204, Q226, Q234, Q252 Q224 Q232 Q203 + Q205 + Q220 + Q210 Q220 + Q245 Q225 + (Q220, Q221)	FAE FAE			<12
4	Q2 + (Q30, Q31, Q32, Q33, Q34, E84, J38, J41, J42, J43, J44, J47, P24, P25, P27, P28 except P283 and P284)	FBL40, FDA, FAE00, FAE10 FA, FB, FC, FD, FE, FF, FG, FH, FI, FJ, FK, FL, FM, FN, FO, FQ, FR, FS, FT, FU, FV, FY, FZ			<12
5	I27, P293B	FA, FB, FC, FD, FE, FF, FG, FH, FI, FJ, FK, FL, FM, FN, FO, FQ, FR, FS, FT, FU, FV, FY, FZ		Only surgery, no diagnosis No diagnosis after surgery Only one diagnosis No surgery and diagnoses only <2 months	<12
6	I42 + I50  FQA, FQB, Z941, Z942, Z943		C03C, C03D, C03CA, C09A, C09C, C07A, C01A, C01CA, C01CE, C01CX, C02KX01, G04BE03, B01AC11	<3 different groups (C03, C09, C07, C01, C02, G04, and B01) during a 3-month period	<12  <24

**Notes:** All criteria on the same row must be fulfilled (logical "and" between columns). If the criteria in a row within an interpretation group are fulfilled, the child is included (logical "or" between rows). Comma (,) means logical "or" and plus (+) means logical "and". \*For definitions of the codes, see the "Supplementary material" section.

The false-negative cases fulfilling the treatment recommendations for palivizumab, but not identified by the algorithm, were further analyzed to find possibilities to improve the algorithm.

### Positive predictive value

For evaluation of the algorithm, the PPV was calculated. Medical records of children captured by the algorithm were identified using information on hospitals and departments from the National Patient Register. The first 34 out of 928 cases generated by the algorithm (random order) were selected for review of their medical records. Given the results of the review, the sample size was assessed to be sufficient. A pediatric cardiologist (GB) analyzed if the criteria for hemodynamically significant CHD, as described by the recommendations for treatment with palivizumab, were fulfilled according to the medical records. A secondary analysis of false-positive cases identified by the algorithm but not meeting

the suggested criteria was performed to investigate if and how the algorithm's exclusion criteria could be enhanced.

### Statistical analysis

All analyses were carried out using SAS<sup>®</sup> software (v 9.3, SAS Institute, Cary, NC, USA).

The recommendations for treatment with palivizumab cover six different indications (target groups), of which a child can have one or more. The algorithm was developed by translating all six indications into logical programming. We denoted these six constructed indications as "interpretation groups". The first interpretation group corresponds to Down syndrome and other chromosomal aberrations, whereas groups 2–6 identify children with hemodynamically significant CHD.

Using the algorithm, all children were independently classified as belonging to at least one of the six interpretation groups. The children in groups 2–6 were then classified as

having hemodynamically significant CHD. The prevalence of hemodynamically significant CHD was calculated as the ratio of children captured by the algorithm to the total number of children by birth year. The distribution of children with hemodynamically significant CHD among interpretation groups was calculated as the respective numbers and proportions. Within each of interpretation groups 2–6, the proportion of children belonging to interpretation group 1 (children with chromosomal aberrations) was also calculated.

For validation of the algorithm, two different samples were chosen. The first sample was used to calculate the sensitivity, and the second was used to calculate the PPV. The sensitivity was defined as the ratio of true positives to the total number of children with CHD according to medical charts. The PPV was defined as the ratio of true positives to the total number captured by the algorithm. Confidence intervals (CIs) for the sensitivity and for the PPV were calculated as 95% exact binomial confidence intervals (95% CIs).

The study was approved by the Regional Ethical Review Board at Karolinska Institute in Stockholm, Sweden.

## Results

### Proposed algorithm and validation

The algorithm for identification of target groups of children with hemodynamically significant heart disease according to indications for palivizumab is presented in a condensed version in Table 2, where the specific ICD-10 and *Anatomical Therapeutic Chemical Classification System* (ATC) codes for inclusion into the interpretation groups are listed. The interpretation groups involved the following different indications for palivizumab.

In interpretation group 1, we included children with Down syndrome, other chromosomal abnormalities, or known immunodeficiency. The children were defined by having at least one of the specified diagnoses of congenital malformations, chromosomal abnormalities, or disorders involving the immune mechanism.

Interpretation group 2 defined children with a left-to-right shunt identified by specific combinations of a diagnosis of congenital heart defects associated surgical or interventional procedure codes and ATC codes for diuretics or agents acting on the renin–angiotensin system.

For interpretation group 3, we defined children with a univentricular heart and children in whom the primary pulmonary blood supply came from a Glenn anastomosis. These children were identified from diagnoses alone, combinations of diagnoses and surgical procedure codes, combinations of diagnoses, or procedure codes alone.

Interpretation group 4 defined children with lung disease and a surgical repair of the heart. To identify these children, we used a diagnosis of congenital malformation of the circulatory system together with at least one of the following: diagnosis of congenital malformation of the respiratory system and/or chronic lower respiratory disease, respiratory, and cardiovascular disorders specific to the perinatal period. Additionally, surgical or interventional procedure codes were included.

In interpretation group 5, we defined children with a diagnosis of idiopathic or persistent pulmonary hypertension and persistent pulmonary hypertension of the newborn with recorded procedure codes for surgery of the heart and major thoracic vessels.

Interpretation group 6 defined children waiting or having had a heart transplant by a recorded diagnosis of cardiomyopathy together with heart failure or codes for heart transplant. These children were also required to have filled prescriptions for at least three different groups of specific cardiovascular drugs during a 3-month period. The complete form of the algorithm is given in the “Supplementary material” section.

Using the algorithm, we identified 928 children with hemodynamically significant CHD born between July 1, 2005 and December 31, 2010. The resulting overall prevalence of hemodynamically significant heart disease based on recommendations for the use of prophylactic treatment with palivizumab was 1.6/1,000 live-born children (Table 3). In addition, 91% of the children identified as having CHD by the algorithm fell into only one of the interpretation groups. Interpretation group 4 (children with structural heart disease plus lung disease) had the most overlap, with 30% of the children classified into at least one of the other interpretation groups. In an extended analysis of background data, 25% of the identified children also had a diagnostic code indicating a chromosomal aberration or syndrome association with extracardial defects (Table 4).

### Validity of the proposed algorithm

#### Sensitivity

A flow chart of the sensitivity analysis is presented in Figure 1. Of the 121 children with known exposition for

**Table 3** Children with hemodynamically significant congenital heart disease identified by the proposed algorithm (yearly prevalence per 1,000 live born)

Year	2005	2006	2007	2008	2009	2010	Total
Prevalence (per 1,000 live born)	1.4	1.6	1.3	1.6	1.8	1.7	1.6

**Table 4** Distribution of children in studied interpretation groups and distribution of children with chromosomal aberrations

Interpretation group	N (%)	Chromosomal aberration (%)
2	365 (39.3)	40
3	201 (21.7)	8
4	137 (14.8)	18
5	127 (13.7)	14
6	14 (1.5)	0
Combination, 2–6	84 (9.1)	31
Total	928 (100.0)	25

palivizumab, 86 cases fulfilled the recommendations for treatment with palivizumab among children with CHD. The algorithm correctly identified 69/86 cases, resulting in a sensitivity of 80% (95% CI 70–88).

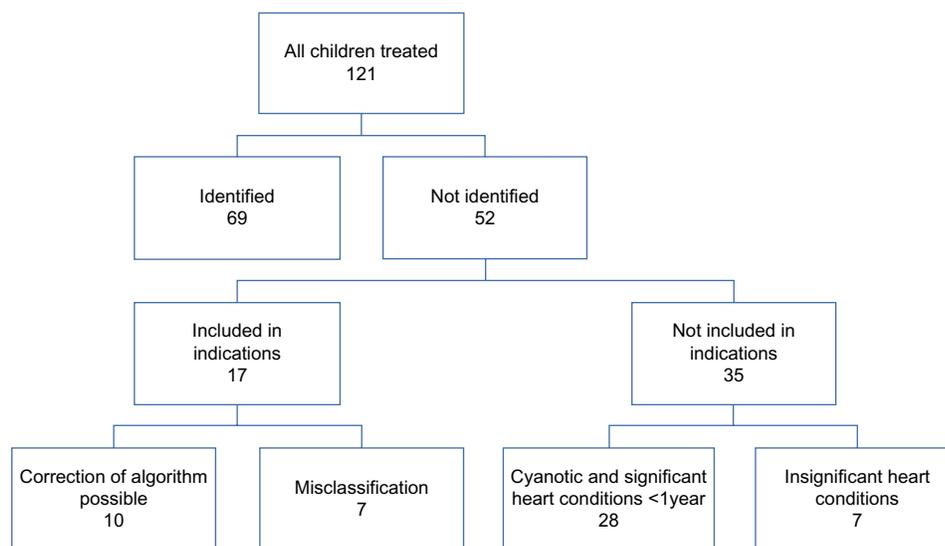
Of children not identified by the algorithm, 17 false-negative cases fulfilled the recommendations for treatment with palivizumab and should have been identified. However, seven (6%) of these were coded with the wrong ICD code in the national registers, and hence were not possible to identify with the algorithm. In the remaining ten cases, we found possibilities to improve the algorithm: to remove the time criterion for surgical/interventional procedures in interpretation group 2 (five cases), but at the cost of a lower PPV; to allow inclusion in interpretation group 3 on surgical criteria only, without a diagnosis of univentricular hearts (one case); and to add three diagnoses or procedure codes (in interpretation group 2: the rare Vein of Galen aneurysm [Q28.2], and the diagnosis of major aortopulmonary collateral arteries [Q27.8] in association

with a surgical or interventional procedure code [FBG]; in Interventional Group 4: the diagnosis of diaphragmatic paresis after surgical treatment for a heart defect [J98.6]). Finally, ATC codes in Interventional Group 6 could be less specific to allow the inclusion of more combinations of pharmacological treatments. Implementing the suggested changes would raise the sensitivity to 92% (95% CI 84–97), given an identical sample.

In the remaining 35 cases, palivizumab was administered outside the existing recommendations. In most cases this was explained by the clinical praxis to treat children with cyanotic heart defects, <1 year of age, prior to corrective heart surgery (n=22); and children with significant and symptomatic heart conditions, including stenotic lesions, prior to or after surgery (n=6). In seven cases the heart condition was found to be insignificant (ie, a moderate and asymptomatic ventricular septal defect without need of treatment).

### Positive predictive value

The PPV of the algorithm was estimated using a sample of 34 children identified by the algorithm randomly selected from 12 different hospitals from Ystad in the south of Sweden to Skellefteå in the northern part of the country. Medical records sufficient for analysis of heart diagnosis and course of the disease were found for all cases. In 79% (6,291) of the analyzed cases, the children were regarded as having hemodynamically significant CHD according to the target groups of the recommendations for treatment with palivizumab.



**Figure 1** Distribution of children treated with palivizumab in relation to identification by the algorithm and whether the case met the indications given in the recommendations for treatment.

A secondary analysis of the seven false-positive cases that did not meet the criteria of the algorithm was performed, with the following results per interpretation group:

- Interpretation group 2 gave a false detection in three cases due to surgically corrected atrial septal defects. In two of these cases, both associated with total anomalous pulmonary venous return, surgery was performed at 4–5 weeks of age after acute diagnosis; that is, these cases did not fulfill the exclusion criterion of surgery below 1 month of age before discharge from hospital. The third of these cases, associated with a coarctation of aorta, surgery was performed at 3 weeks of age. However, the algorithm's exclusion criterion of surgery below 1 month of age also stated that it should be performed before discharge, which did not apply because of missing discharge date in the national registers.
- Interpretation group 3 generated one case of erroneous use of ICD-10 code Q23.4 (hypoplastic left heart syndrome) to describe a physiological small left ventricle in association with coarctation of the aorta that was surgically corrected at 10 days of age.
- Interpretation group 4, focusing on children with significant lung disease and a corrected heart defect, generated two false inclusions that should be excluded in an updated algorithm: spontaneously resolving apnea of the newborn (ICD-10 code P28.3) and nonallergic asthma (ICD-10 code J45.1). The latter is often used in the case of an acute viral airway infection complicated with hyperreactivity and wheezing.
- Interpretation group 5 generated one false case with a mild course of persistent pulmonary hypertension resolving with the last date of diagnosis just after 2 months of age. An extended analysis of the total interpretation group 5 (127 children) yielded 15 children with last diagnosis between the ages of 2 and 3 months. Among these, two children were exposed to palivizumab.
- Interpretation group 6 was not represented in the sample.

## Discussion

We have shown that it was possible to identify a subgroup of children with hemodynamically significant CHD by using an epidemiological approach and an algorithm with high validity.

The validation procedure demonstrated a high sensitivity of approximately 80% for the algorithm, and medical record review found the algorithm to generate a PPV of 79%, which is comparable to other algorithms for complex

clinical conditions.<sup>7</sup> Furthermore, we outlined how an increase in sensitivity can be achieved by some simple changes to the algorithm. However, the sensitivity of an algorithm for epidemiological research based on the reporting of clinical diagnoses to registers will always be limited because of misclassification due to erroneously coded diagnoses, which in our study was 6%. This is a low rate compared with those of studies of other algorithms within the epidemiological field,<sup>7</sup> which in part may be attributable to a rather restricted patient group managed by physicians specialized within the field.

Our study also confirmed that the vast majority of children treated with palivizumab had a clinically and hemodynamically significant heart disease. Most of the children fulfilled the criteria described by the recommendations. However, the clinical praxis of treating children with cyanotic heart defects and other complex situations was confirmed. From the point of view of creating an algorithm to also identify this group, we found it possible to add an interpretation group if necessary, based on the actual ICD-10 codes associated with certain surgical and interventional procedure codes, in line with the existing algorithm.

The validity of the proposed algorithm in regard to the PPV must be assessed in light of its purpose. Used in a nationwide, epidemiologic setting for identification of a cohort of children with birth defects at risk of exposure to palivizumab, we find the validity fully adequate for our purpose. Furthermore, our analysis of false-positives demonstrates possible ways to enhance the algorithm by adjusting the exclusion criteria, in particular concerning discharge date, age, and particular diagnoses. By adjusting the exclusion criteria it is possible to increase the PPV but at the cost of a lower sensitivity, because the changes decrease both the number of false-positives and the number of true negatives. Misclassification of the studied diagnoses by erroneous use of the ICD-10 codes in medical records from different parts of the country was seen in only one of the 86 studied cases and seemed to be a minor problem in this cohort.

The prevalence generated in this study (Table 3) is in line with calculated estimates used in the Swedish planning and recommendations for the use of palivizumab.<sup>8</sup> However, it should be noted that the children identified in this study were a subset of children with major heart defects (defined as being in need of surgical or catheter interventional treatment within the first year of life), which comprises 3–4 per 1,000 live-born children.<sup>9–11</sup> The reason for this is the early treatment, often within the first month of life, for a range of major heart defects (eg, duct-dependent CHD), relieving the child from hemodynamically significant consequences.

It should also be noted that the proportion treated with palivizumab is expected to be smaller due to variations in the season of respiratory syncytial virus infection and in the clinical course of the heart disease, as well as the clinical coverage and acceptance of the treatment. In addition to the prevalence figures, the algorithm generated an association with chromosomal anomalies and syndromes in 25% of the cases, in line with previous epidemiological studies,<sup>9</sup> possibly indicating a representative case mix of major hemodynamically significant CHD.

The strength of this study is its demonstration of the feasibility of creating a validated algorithm for identifying a complex cohort in register-based research. Furthermore, the proposed algorithm to identify children with hemodynamically significant CHD was validated with medical records as the gold standard. Due to the lack of the true numbers of the studied target groups for calculating the sensitivity, we used local data from two hospitals on all children treated with palivizumab as an equivalent, which necessitated including cases not targeted by the recommendations. This sample size represented more than 25% of all children born in Sweden and was therefore deemed adequate, although the small number of hospitals still could be a limitation.

A general limitation of the use of an algorithm as proposed is the fact that data in national registries are not collected primarily for research purposes. Hence, data cleaning, checking of data quality, and handling of outliers are important, though not all problems inherent in the data can be solved by those procedures. It is also a general limitation of the Prescribed Drug Register that medication administered in-hospital without a prescription is not included. However, the exposure in this study was not affected by this limitation because we used local hospital data to identify children exposed to palivizumab. One possible limitation of the algorithm was that it used filled prescriptions to identify children with hemodynamically significant CHD.

## Conclusion

We have shown that it is possible to identify a subgroup of children with hemodynamically significant CHD through an epidemiological approach. By linking diagnostic, surgical, and interventional codes with specific criteria for dispensing of prescribed drugs and age, we described an algorithm with high validity for the identification of children with hemodynamically significant CHD. This will allow subsequent analyses on similar populations to be more precise and clinically relevant. Additionally it will enable well-powered

national cohort studies of individuals with complex clinical conditions.

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## Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

Lone Graff Stensballe hold grants for a research initiated study from AbbVie. Helle Kieler, Marie Linder, Gunnar Bergman, and Ann Hærskjold have worked on a research project sponsored by AbbVie. The company had no role in the data collection or analysis for this study and was not involved in the interpretation of results, writing, revision, and approval of the manuscript.

The authors report no other conflicts of interest in this work.

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## Supplementary material

Algorithms to identify children with hemodynamic significant heart disease according to national Swedish recommendations for treatment with palivizumab (Table 1). Information was obtained from the national health registers. Conditions were defined using a combination of codes from the *International Classification of Diseases (ICD-10)*, *Nordic Classification of Surgical Procedures 1997, revised 2004*, and recording of pharmacological treatment by the *Anatomical Therapeutic Chemical Classification System*.

1. Infants below 6 months of age with a significant heart disease and Down syndrome or other chromosomal abnormality or known immunodeficiency or significant syndrome
  - Chromosomal abnormalities, not elsewhere classified (Q9)
  - Congenital malformation syndromes due to known exogenous causes, not elsewhere classified (Q86)
  - Other specified congenital malformation syndromes affecting multiple systems (Q87)
  - Other congenital malformations, not elsewhere classified (Q89)
  - Immunodeficiency with predominantly antibody defects (D80)
  - Combined immunodeficiencies (D81)
  - Immunodeficiency associated with other major defects (D82)
2. Infants below 6 months of age with left-to-right shunt. Diagnoses, procedures, and filling of prescriptions must appear before 6 months of age. Infants who have had surgery at or before 1 month of age are not included
  - Ventricular septal defect (Q210) and diuretics (C03) *or* agents acting on the renin–angiotensin system (C09) and
    - Closure of isolated congenital ventricular septal defect (FHB) *or*
    - Closure of multiple congenital ventricular septal defects (FHC) *or*
    - Banding operations on pulmonary artery (FBC)
  - Atrial septal defect (Q211) and diuretics (C03) *or* agents acting on the renin–angiotensin system (C09) and closure of isolated atrial septal defect (FFC)
  - Atrioventricular septal defect (Q212) and diuretics (C03) *or* agents acting on the renin–angiotensin system (C09) and
    - Repair of complete atrioventricular septal defect (FHD) *or*
    - Operations for partial atrioventricular septal defect (FFD) *or*
    - Banding operations on pulmonary artery (FBC)
  - Aortopulmonary septal defect (Q214) and diuretics (C03) *or* agents acting on the renin–angiotensin system (C09) and closure of congenital fistula from aorta (FDD10, FDD13, FDD20)
  - Patent ductus arteriosus (Q250) and diuretics (C03) *or* agents acting on the renin–angiotensin system (C09) and closure of patent ductus arteriosus (FDE)
3. Infants under 12 months of age with a univentricular heart or children where the primary pulmonary blood supply comes from a Glenn anastomosis. Diagnoses or procedures must appear before 12 months of age
  - Double inlet ventricle (Q204)
  - Hypoplastic right heart syndrome (Q226)
  - Hypoplastic left heart syndrome (Q234)
  - Atresia of aorta (Q252)
  - Discordant ventriculoarterial connection (Q203) and discordant atrioventricular connection (Q205) and pulmonary valve atresia (Q220) and ventricular septal defect (Q210)
  - Pulmonary valve atresia (Q220) and malformation of coronary vessels (Q245)
  - Ebstein's anomaly (Q225) and pulmonary valve atresia (Q220)
  - Ebstein's anomaly (Q225) and congenital pulmonary valve stenosis (Q221)
  - Congenital tricuspid stenosis (Q224) and connection to pulmonary artery from superior vena cava (FAE)
  - Congenital mitral stenosis (Q232) and connection to pulmonary artery from superior vena cava (FAE)
  - Aortopulmonary anastomosis in single ventricle conditions (FBL40)
  - Surgery for hypoplastic left heart syndrome (FDA)
  - Anastomosis to pulmonary artery from superior vena cava (FAE00)
  - Bidirectional anastomosis between superior vena cava and pulmonary artery (FAE10)
4. Infants below 12 months of age with structural heart disease and lung disease, and having had surgical heart repair before 12 months of age. Diagnoses or procedures must appear before 12 months of age
  - Congenital malformations of the circulatory system (Q2) and
    - Congenital malformations of nose (Q30)

- Congenital malformations of larynx (Q31)
  - Congenital malformations of trachea and bronchus (Q32)
  - Congenital malformations of lung (Q33)
  - Other congenital malformations of respiratory system (Q34)
  - Cystic fibrosis (E84)
  - Diseases of vocal cords and larynx, not elsewhere classified (J38)
  - Chronic lower respiratory diseases except asthma (J40–J44, J47)
  - Neonatal aspiration syndromes (P24)
  - Interstitial emphysema and related conditions originating in the perinatal period (P25)
  - Chronic respiratory disease originating in the perinatal period (P27)
  - Other respiratory conditions originating in the perinatal period (P28), except for apnea (P283, P284) and
    - Surgery of heart or major thoracic vessels (FA, FB, FC, FD, FE, FF, FG, FH, FI, FJ, FK, FL, FM, FN, FO, FQ, FR, FS, FT, FU, FV, FY, FZ)
5. Infants below 12 months of age with pulmonary hypertension and having had heart surgery. Diagnoses or procedures must appear before 12 months of age. Those recorded with pulmonary hypertension as a single diagnosis before 2 months of age are not included. Infants recorded with a surgical procedure must have at least one diagnosis recorded after the procedure
- Pulmonary hypertension (I27) at two occasions or more
  - Persistent pulmonary hypertension of the newborn (P293X\*) on two or more occasions
  - Surgery on heart or major thoracic vessels (FA, FB, FC, FD, FE, FF, FG, FH, FI, FJ, FK, FL, FM, FN, FO, FQ, FR, FS, FT, FU, FV, FY, FZ) followed by a diagnosis of pulmonary hypertension (I27 or P293X)
6. Infants below 12 months of age with a diagnosis of cardiomyopathy and heart failure who are on triple medication. Diagnoses, procedures, or filling of prescriptions must appear before 12 months of age. Children with a heart transplant before 2 years of age are also included
- Cardiomyopathy (I42) and heart failure (I50) with a combination of drugs from at least three drug classes (B01, C01–3, C07, C09, G04) during a 3-month period.
    - B01
      - Iloprost (B01AC11)
    - C01
      - Cardiac glycosides (C01A)
      - Adrenergic and dopaminergic agents (C01CA)
      - Phosphodiesterase inhibitors (C01CE)
      - Other cardiac stimulants (C01CX)
    - C02
      - Bosentan (C02KX01)
    - C03
      - High-ceiling diuretics (C03C)
      - Potassium-sparing agents (C03D)
      - Low-ceiling diuretics, thiazides (C03A)
    - C07
      - Beta-blocking agents (C07A)
    - C09
      - Angiotensin-converting-enzyme inhibitors, plain (C09A)
      - Angiotensin II antagonists, plain (C09C)
    - G04
      - Sildenafil (G04BE03)
  - Transplantation of heart (FQA)
  - Transplantation of heart and lung (FQB)
  - Heart transplant status (Z941)
  - Lung transplant status (Z942)
  - Heart and lungs transplant status (Z943)
- Note:** \*X denotes national subcode.

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