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FORMAL EVIDENCE-BASED AND EXPERT CONSENSUS ON IMMUNOPROPHYLAXIS WITH PALIVIZUMAB IN PATIENTS WITH CONGENITAL HEART DISEASE

CONSENSO FORMAL BASADO EN LA EVIDENCIA Y OPINIÓN DE EXPERTOS EN INMUNOPROFILAXIS CON PALIVIZUMAB EN PACIENTES CON CARDIOPATÍA CONGÉNITA

Órgano oficial de la Asociación
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Formal evidence-based and expert consensus on immunoprophylaxis with palivizumab in patients with congenital heart disease

SUMMARY

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Consenso formal basado en la evidencia y opinión de expertos en inmunoprofilaxis con palivizumab en pacientes con cardiopatía congénita

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Presentation

Presentación

Darío Echeverri[1*]

[1] *Editor-in-Chief, Revista Colombiana de Cirugía.*

On behalf of Sociedad Colombiana de Cardiología y Cirugía Cardiovascular and its official organ, Revista Colombiana de Cardiología, we would like to recognize Dr. Mónica Guzmán Bustamante as the Guest Editor of the current supplement titled "Formal evidence-based and expert consensus on immunoprophylaxis with palivizumab in patients with congenital heart disease", along with all the distinguished authors of its various chapters, for their great effort in achieving this special edition made up of various topics addressed with great expertise and scientific caliber.

Respiratory syncytial virus is a very important cause of acute respiratory infections in children around the world, as well as one of the viruses most frequently studied by the scientific community. The humoral immune response, along with the T-cell mediated cellular response, are vital for effective host defense. Natural infection does not provide lasting immunity against the infection; therefore, reinfections are common throughout life. This document will review several aspects of the virus, the pathophysiology of the infection and the guidelines for prevention with immunoprophylaxis.

Thus, this special edition provides crucial information for preventing respiratory syncytial virus infections in patients with congenital heart disease.

Once again, we offer our sincere thanks to the authors who have kindly contributed to this issue, for all their effort and time invested.

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Prologue

Prólogo

Mónica Guzmán-Bustamante[1,2]

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Over the years, important changes have occurred in the way in which decisions are made that lead to therapeutic processes in health care and especially in the field of pediatric cardiology. We have changed from a medical practice in which the physician, as an individual, with his/her personal expertise and perception of the patient, would devise a treatment aimed at a more homogenous medical practice in both its approach and its goals and, therefore in its outcomes. This change seeks to benefit most sick people and, at the same time, harmonize the care they are offered. This is how we arrived at evidence-based medicine, providing a new way of evaluating and conducting medical practice. The days of individualistic physicians are gone, and we have advanced toward the creation and harmonization of concepts that allow joint work toward a common goal: to care for and heal our patients.

The publication of this formal evidence-based expert consensus on immunoprophylaxis with palivizumab in patients with congenital heart disease arises from the need to protect and thus positively impact on the care of our pediatric patients under the age of two who have hemodynamically significant congenital heart disease.

This document also seeks to strengthen the awareness of teamwork which, in turn, leads to egalitarian behavior which is key for the future of the population under our care and for creating working groups to benefit all Colombian regions. Therefore, the selection of people for this job was crucial, with the objective of covering a representative area of all our regions, considering regional differences in thinking and acting as well as the varying availability of medications as essential factors in constructing the foundations of this project. Furthermore, an approach is needed to nuance and harmonize the means and the ends within the framework of pediatric cardiology care, seeking a balance to open new opportunities through a combination of solidarity, collegiality and effort.

As pediatric cardiologists, we are increasingly concerned with developing projects such as this one, created based on an ethical and academic approach within an epidemiological framework which allows us to progress toward a better protection of our target population.

In this regard, and as will be analyzed in this consensus, we pediatric cardiologists needed to set aside our individualistic opinions and approaches, and instead, supported by a qualified group of epidemiologists, create a working group which, by producing clear concepts regarding the use of palivizumab in heart disease patients, would benefit the clinical practice of all the professionals: neonatologists, high-risk pediatricians, general pediatricians, intensivists, pulmonologists, immunologists and, in general, all the actors that are essential in the care of heart disease patients.

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This project began in May 2022, when we approached the group of epidemiologists (Odds Epidemiology) that would guide us through this project. Then, the first team of pediatric cardiologists was created with the following physicians: Oscar Arévalo (Fundación HOMI, Bogotá), Alejandra Portilla (Centro Pediátrico y Cardiológico del Cauca, Popayán), Antonio Madrid (Hospital Universitario del Valle, Cali), Arnaldo Palomino-Rodríguez (Hospital Serena del Mar, Cartagena), Luis E. Ponce-Bravo (Hospital Infantil Los Ángeles, Pasto), Olga Maza-Caneva (Organización Clínica General del Norte, Barranquilla), Sandra Flórez (Hospital Universitario Erasmo Meoz, Cúcuta) and myself, Mónica Guzmán-Bustamante (Clínica CardioVID, Medellín), who met in person in September of that same year and drafted the first questions which would be the basis for future recommendations on the use of palivizumab in patients with congenital heart disease. Subsequently, to validate the Consensus, we added the following physicians to this project: Heidy Barrios (Clínica Portoazul, Barranquilla), Javier Castro-Monsalve (Fundación Cardiovascular de Colombia, Bucaramanga), Jaime Franco (Fundación A. Shaio, Bogotá), Tatiana Padilla (Clínica El Rosario, Medellín), Iván A. Pinto-Martínez (Fundación Cardiovascular de Colombia, Bucaramanga), Claudia Stapper (Fundación Cardioinfantil, Bogotá) and Aída Figueroa-Reyes (Clínica IMAT Oncomédica Auna, Montería). After evaluating the quality of the evidence and the strength of the recommendations with this additional group of physicians, we determined that the certainty of the evidence ranged from low to moderate, the score was often lowered by the risk of bias and imprecision, and the favorable recommendations indicated that the desirable consequences probably outweigh the undesirable consequences. Thus, the most important elements for this decision are those pertaining to the ratio of the effect size to social availability and cost.

The result of all this work carried out over almost 18 months is a consensus which we hope will serve as a guide for decision making in the use of immunoprophylaxis with palivizumab for patients with congenital heart disease. We expect that this will benefit physicians not only in Colombia, but also in neighboring countries and, ultimately, support the good clinical judgement with which our colleagues carry out their work of caring for our children.

Finally, we would like to especially thank AstraZeneca for their unconditional support, as well as our epidemiologists who, with their patience and knowledge, led us to this result. Thanks to the Sociedad Colombiana de Cardiología y Cirugía Cardiovascular for their diligence, support and commitment in the search for new tools to impact on the cardiovascular health of our patients; and, finally, thanks to all our colleagues who kindly lent a hand to support this Consensus, which arises from a few to benefit many.

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SPECIAL ARTICLE

Formal evidence-based and expert consensus on immunoprophylaxis with palivizumab in patients with congenital heart disease

Consenso formal basado en la evidencia y opinión de expertos en inmunoprofilaxis con palivizumab en pacientes con cardiopatía congénita

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Abstract

Introduction. *Infants with congenital heart disease (CHD) constitute a patient cohort at risk of serious infections due to respiratory syncytial virus. The rate of respiratory infection complications in these patients is high compared with other groups. Given the high staff and economic burden of respiratory syncytial virus infection in high-risk groups, prevention of this infection is recommended.* ***Method***. *The document was constructed in the following stages: a) defining the research questions; b) searching for, screening, evaluating and selecting the evidence; c) synthesizing the evidence to answer the research questions; d) conducting a GRADE evaluation; e) discussing in formal panels; f) establishing recommendations and expert opinion; and g) drafting, developing and reviewing the consensus document.* ***Results***. *The 15 participants arrived at a consensus and framed 16 recommendations which, over the course of the consensus, were combined to ultimately leave 13. The certainty of the evidence ranged from low to moderate; the rating was lowered by the risk of bias and imprecision, and the recommendations were weakly in favor, indicating that the desirable consequences probably outweigh the undesirable consequences. The most important elements for this decision were the ratio of the effect size to damage, social availability and cost.* ***Conclusion***. *The recommendations should serve as a guideline to facilitate immunoprophylaxis in infants with congenital heart disease. As new evidence emerges, these recommendations may need to be reconsidered and carefully reviewed.*

Keywords: *Congenital heart disease. Palivizumab. Respiratory syncytial virus. Congenital heart defects.*

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Resumen

Introducción. *Los lactantes que sufren cardiopatías congénitas representan una cohorte de pacientes en riesgo de infecciones graves causadas por el virus sincitial respiratorio. Las tasas de complicaciones de las infecciones respiratorias en estos pacientes son más altas comparadas con otros colectivos. Dada la importante carga personal y económica de la infección por el virus sincitial respiratorio en grupos de alto riesgo, se recomienda prevenir la infección.* ***Método***. *La construcción del documento se desarrolló en las siguientes etapas: a) definición de las preguntas objeto de investigación, b) búsqueda, tamización, evaluación y selección de la evidencia; c) elaboración de síntesis de la evidencia dando respuesta a las preguntas objeto de investigación; d) evaluación GRADE; e) discusión en paneles formales, f) generación de recomendaciones y juicio de expertos y g) redacción, elaboración y revisión del documento de consenso.* ***Resultados***. *Los 15 participantes llegaron a un consenso y formularon 16 recomendaciones las cuales en el desarrollo del Consenso se fusionaron y quedaron finalmente 13. La certeza de la evidencia varió entre baja a moderada; la valoración disminuyó por riesgo de sesgo e imprecisión, y las recomendaciones fueron débiles a favor, indicando que las consecuencias deseables probablemente sobrepasan las consecuencias indeseables. Los elementos más importantes para esta decisión correspondieron a la relación magnitud del efecto y daño; disponibilidad social y costo.* ***Conclusión***. *Las recomendaciones formuladas deben servir como una pauta para facilitar la inmunoprofilaxis en lactantes con cardiopatías congénitas. A medida que surja nueva evidencia, es posible que sea necesario reconsiderar y revisar cuidadosamente estas recomendaciones.*

Palabras clave: *Cardiopatías congénitas. Palivizumab. Virus sincitial respiratorio. Defectos cardíacos congénitos.*

Introduction

Acute respiratory infections are one of the main causes of morbidity and mortality in children under the age of five, and respiratory syncytial virus (RSV) is the most common causal agent[1]. Worldwide, RSV is the most common cause of acute respiratory tract infections (ARTIs) in children, with at least 3.4 (95% CI: 2.8-4.3) million episodes requiring hospitalization each year[2]. Based on small amounts of prospective surveillance data, we know that most children have been infected by the virus by age two (including two or more episodes in up to 42% of children at this age)[3].

Likewise, RSV infection causes a variety of diseases like bronchiolitis and pneumonia, with a clinical presentation ranging from mild to severe. In most cases, RSV disease is self-limited; however, some newborns or infants may require hospitalization and experience severe morbidity and early mortality. Due to their clinical conditions, babies with congenital heart disease (CHD) are at high risk of developing complications related to RSV infection and, therefore, have a greater risk of hospitalization. The severe acute forms may need strict monitoring for long-term morbidity control[4]. Congenital heart disease not only raises the morbidity and mortality rates in these children, but also the treatment costs, due to more intensive care unit admissions, and longer oxygen therapy and mechanical ventilation[5].

Certain associated clinical conditions increase the morbidity of acute respiratory infections, including some cardiovascular factors like increased pulmonary vascular resistance and congenital heart disease with hemodynamic repercussions. The factors associated with CHD include abnormal lung mechanics secondary to increased or decreased pulmonary flow, which causes an abnormal ventilation/perfusion balance leading to decreased pulmonary compliance and increased airway resistance[6].

Congenital heart disease refers to a group of diseases in which the heart and/or great vessel structures are abnormal at birth, which can have varying effects on blood circulation patterns as well as decrease the ability to compensate for infection, with altered oxygen distribution caused by the respiratory infection[1].

Congenital heart disease is the most common type of birth defect; it accounts for one third of all significant congenital anomalies and is therefore a significant global health problem[7]. The overall reported prevalence of CHD has increased over the last century, probably due to improved diagnostic methods and detection modalities[7]. Likewise, this overall prevalence increased over time, from 0.6 per 1,000 live births (95% IC: 0.4-0.8) between 1930 and 1934, to 9.1 per 1,000 live births (95% CI: 9.0-9.2) after 19958. The figure has stabilized over the last 15 years, corresponding to 1.35 million newborns with CHD every year[8,9]. Epidemiological studies have shown that early diagnosis and treatment can significantly improve the prognosis of newborns with CHD. It is also the main cause of death in perinatal infants and children under the age of five10.

Therefore, inadequate treatment during the first year of life leads to high mortality[9].

In South America, CHDs occur in 28 cases per 10,000 live births, giving rise to approximately 54,000 cases per year[11], 41,000 of which require some type of treatment; however, sadly, only 17,000 undergo surgery[9]. In Colombia, they are the third most common congenital malformation (1.6-2.0 per 1,000 live births), accounting for 17% of all congenital anomalies, with most being ventricular septal defects, although there is significant underreporting due to CHDs not detected at birth[12].

Congenital heart disease reduces the infant's ability to increase cardiac output, and, at the same time, the oxygen supply may be severely restricted. If an infant develops an acute lower respiratory infection (ALRI) due to RSV, oxygen consumption can be even more affected. In these infants with a limited cardiac reserve, respiratory work increases, resulting in a particular risk of severe disease and hospitalization, in some cases requiring intensive care unit (ICU) admission, supplementary oxygen and prolonged mechanical ventilation[13].

In addition, RSV ALRIs can cause death in the time frame immediately around palliative or corrective heart surgery with extracorporeal circulation[7]. The prognosis of surgical CHD treatment is poor when surgery is performed before complete recovery from RSV infection, or if the patient undergoes surgery with an active infection, in which case postoperative pulmonary hypertension plays an important role in mortality[14].

Hemodynamically significant congenital heart disease (HS-CHD) coupled with RSV infection may lead to prolonged hospitalization[15] and a higher risk of death[16]. Respiratory syncytial virus infection may also delay corrective heart surgery[17] and potentially increase the morbidity associated with CHD[7]. It has also been associated with a 3.7 times greater risk of death (95% CI: 2.71-5.25) in infants hospitalized for RSV[18].

To date, there is no specific treatment for RSV infections and disease management is based on controlling the symptoms, although severe forms require support measures like oxygen supplementation or other respiratory assistance[19]. Therefore, the best strategy to limit the spread of RSV infections and protect patients at risk of severe complications[4] is strict adherence to the RSV prophylaxis recommendations[13], such as preventive immunization strategies[4], which are the only modifiable protective factor for decreasing ARI hospitalization rates[13].

There is no pediatric RSV vaccine available today[20]. The essay published by the American Academy of Pediatrics (AAP) in 2003[21] recommended the use of palivizumab, an mAb that recognizes an antigenic site of the RSV F glycoprotein[4], and these guidelines on palivizumab have been updated four times since then, as more data have become available to provide a better understanding of infants and small children with a higher risk of hospitalization due to RSV infection. The recommendations in the 2014 statement indicated that the children with HS-CHD with a higher probability of benefiting from immunoprophylaxis include infants with acyanotic disease who are on medications to control congestive heart failure and will require heart surgery, as well as infants with moderate to severe pulmonary hypertension[22].

Background or justification

Lower respiratory tract infection due to RSV may be severe in infants and places a substantial medical and financial burden on pediatric healthcare services and families around the world[23]. It is known to infect almost all children by two years of age, and the risk of severe disease increases in certain well known high-risk groups, such as those with CHD[23,24]. A systematic review and meta-analysis in 2020 showed a higher risk of severe RSV (OR: 2.2; 95% CI: 1.6-2.8), hospitalization rate (incidence rate ratio: 2.8; 95% CI: 1.9-4.1) and case fatality rate (RR: 16.5; 95% CI: 13.7-19.8) associated with RSV-LRTI in children with underlying CHD, compared with those without CHD. The risk of ICU admission (RR: 3.9; 95% CI: 3.4-4.5), need for supplementary oxygen (RR: 3.4; 95% CI: 0.5-21.1) and need for mechanical ventilation (RR: 4.1; 95% CI: 2.1-8.0) were also higher in children with underlying CHD[25].

Respiratory syncytial virus accounts for more than 30 million new LRTIs per year worldwide, leading to 3.2 million hospital admissions and almost 60,000 deaths in children under the age of five26. Respiratory syncytial virus infections cause 16 times more hospitalizations and emergency room visits in children under the age of five than infections caused by the flu virus[27].

Respiratory syncytial virus infections not only cause more hospitalizations but can also have negative long-term effects on children's health27. A systematic review including prospective epidemiological studies consistently showed that RSV LRTI is a significant risk factor for ongoing respiratory morbidity, characterized by early transient and recurrent wheezing and asthma during the first decade of life and possibly through adolescence and into adulthood (high strength of evidence [SOE]); RSV was also associated with deteriorated pulmonary function in this population (high SOE)28. These long-term consequences can have negative effects on the overall quality of life of children and their families[27].

What is more, RSV is recognized as the main cause of pediatric hospital admissions in the United States, according to a study done more than 20 years ago[29]. In its latest update in August 2023[30], the National Center for Immunization and Respiratory Diseases (NCIRD) stated that an estimated 58,000 to 80,000 children under the age of five are hospitalized every year in the United States due to RSV infection. Every year, RSV is responsible for approximately 500,000 emergency room visits and 1.5 million outpatient visits[31].

The evidence has also consistently shown that premature babies and children with chronic diseases and pulmonary diseases (bronchopulmonary dysplasia or HS-CHD) have a higher risk of severe RSV disease[32,33].

In Colombia, a multicenter, noncomparative prospective observational study in six Colombian cities (Barranquilla, Bucaramanga, Cali, Medellín, Cartagena and Pereira) enrolled 600 patients, 6.9% (n = 41) of whom had hemodynamically significant acyanotic and cyanotic CHD (hypertension or medically treated heart failure). Each patient was followed during immunoprophylaxis over a recruitment period of two years. Prophylaxis was administered monthly during the RSV season, with a maximum of five doses. Altogether, 53.3% (n = 318) received three or more doses of palivizumab. The mean interval beteween doses was 39.6 days. Eleven patients (1.8%) were hospitalized for confirmed RSV infection. Overall mortality was 1.2% (7/596) and there were 88 hospitalizations. Specific RSV mortality in infants who received prophylaxis was 0.2% (1/596) due to superinfected bronchiolitis. During the study, a total of 103 adverse events were reported, 95 (92.2%) of which were serious, while the other 8 (7.7%) were reported as not serious. The authors concluded that palivizumab was a clinically effective and well tolerated treatment in the Colombian population[34].

The mechanisms of this increased morbidity are not fully understood, and the studies suggest that, in addition to immature or underdeveloped lungs, an unregulated immune response could play a role. In fact, young infants with RSV infection had less interferon in their blood and mucous membranes than older infants (> 6 months), which was related to longer hospital stays and more extended supplementary oxygen use[35].

Respiratory syncytial virus infection is associated with substantial morbidity in children, both in hospital and ambulatory settings. Studies have also shown RSV infection in previously healthy children, which suggests that control strategies aimed only at high-risk children will have a limited effect on the overall burden of disease from this viral infection[6].

However, the high burden of disease associated with RSV emphasizes the need to develop safe and effective preventive and therapeutic interventions[33]. Since 1998, the humanized monocolonal antibody palivizumab continues to be the only available authorized option for preventing severe RSV disease in high-risk children; that is, premature babies and those with chronic lung disease and CHD[33].

Passive immunization with palivizumab has been recommended as passive prophylaxis for high-risk infants[24]; however, therapeutic efficacy depends on patient adherence[36]. The Canadian palivizumab registry (CARESS)[36], made up of 19,235 infants who received a total of 83,447 injections between October 2005 and May 2014, indicates that palivizumab adherence was significantly associated with a lower incidence of RSV (RR: 0.74; 95% CI: 0.60-0.93; p = 0.01). It was not significantly associated with RSV hospitalization, but was significantly associated with the incidence of intubation, the length of hospital stay, length of intensive care stay and respiratory assistance. Thus, these authors concluded that adherence may have implications for children with less severe RSV infections and those who are already hospitalized for RSV infection[36].

Since there is no guideline or clinical practice guideline in Colombia that indicates the norms for palivizumab use in patients with CHD and this is left to the discretion of each attending physician, the Sociedad Colombiana de Cardiología y Cirugía Cardiovascular decided to conduct a formal consensus to establish evidence-based recommendations and an expert consensus for palivizumab administration, considering the recent data on the burden of morbidity from RSV disease, and the effectiveness and safety of palivizumab in infants with CHD at risk of severe RSV disease.

Method

The method for drafting the recommendation consensus document included specifying research questions using the PICO model.

- Population: children ≤ 24 months old with HS-CHD.
- Intervention: immunoprophylaxis with palivizumab.
- Comparator: placebo or no prophylaxis.
- Principal outcomes.

The primary evaluation criterion included hospitalization for RSV infection or out-of-hospital mortality secondary to RSV.

The secondary evaluation criteria included length of hospital stay, duration of intubation and time in the ICU related to RSV infection.

- Context: middle-income country

- Perspective: population
- A systematic literature search was performed in ClinicalKey, Cochrane, EBSCOhost, Embase/PubMed, Epistemonikos, ScienceDirect and Web of Science using MeSH and DeCS terms; the selected terms were combined using logical Boolean operators (OR, AND, NOT). A manual search (Google Scholar) of the references included in the selected articles was also performed. Primary and secondary publications for which full text was available were considered. The following were excluded: a) studies related to non-target populations or outcomes; b) studies with fewer than 50 participants; c) case reports, cases series and opinion articles; and d) documents published in languages other than Spanish or English.

Following the search, all the documents found in the different databases were uploaded to the bibliographic manager EndNote X9; after this, duplicates were eliminated, the articles that did not meet the inclusion criteria were excluded and screening was conducted. The bibliographic references in the articles found were reviewed to identify literature that was not captured in the search of the specified data sources.

Screening was done by pairs with double blinding using the Rayyan tool (included, excluded, undecided), based on a reading of article titles and abstracts. Likewise, the content of the articles was explored to evaluate whether they met the inclusion criteria. Undecided results were resolved through discussion until agreement was reached. Articles whose titles or abstract were unclear were reviewed based on the selection criteria through a full-text review.

Various internationally validated instruments were used to evaluate the methodological quality of the selected studies, depending on their design, such as AMSTAR, the Newcastle-Ottawa Scale (NOS) and the Cochrane Collaboration's risk-of-bias tool. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to evaluate the certainty of evidence by domains (risk of bias, imprecision, inconsistency, indirectness and publication bias), with scores ranging from high to very low (Table 1), and the input documents for devising the recommendation proposal were developed using narrative evidence synthesis.

As our objective is to provide valid practical recommendations, for which an acceptable methodological quality of the evidence is an essential prerequisite, the following criteria were established for the best-evidence synthesis:

Strong evidence - A	≥ 2 high-quality studies ≥ 75% consistent findings in these studies
Moderate evidence - B	1 high-quality study and/or ≥ 2 moderate-quality studies ≥ 75% consistent findings in these studies

Table 1. GRADE system; levels of evidence.

Score	Grade	Definition
A	High	The authors have a lot of confidence that the real effect is similar to the estimate. The evidence includes a meta-analysis, a high-quality systematic review or a clinical study with a low risk of bias.
B	Moderate	The real effect is probably close to the estimated effect, but it may be substantially different. The evidence includes a systematic review or cohort studies with a low risk of bias and a high likelihood of a causal relationship.
C	Low	There is limited confidence in the estimated effect: the real effect could be substantially different from the estimate. The evidence includes cohort studies with a low risk of bias and a medium likelihood of a causal relationship.
D	Very low	There is very little confidence in the estimated effect: the real effect is likely to be substantially different from the estimate. The evidence includes cohort studies with a high risk of bias or expert opinions.

Adapted from: *Aguayo-Albasini JL, Flores-Pastor B, Soria-Aledo V. Sistema GRADE: clasificación de la calidad de la evidencia y graduación de la fuerza de la recomendación. Cirugía Española 2014;92(2):82-8; Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.*

Limited evidence - C	1 moderate-quality study and/or ≥ 1 low-quality study
Contradictory evidence - D	≥ 2 studies of any quality
	< 75% consistent findings in these studies
No evidence	No eligible studies were found

A formal consensus was developed using the modified Delphi method, through virtual meetings via Teams with 15 participants. In each round, the experts engaged in analysis and discussion, taking into account both their experience as well as the scientific evidence provided by the systematic literature review of each of the established questions, reaching conclusions and recommendations on the topic discussed. These conclusions and recommendations were voted on by the panel using a three-item scale: agree, disagree and undecided. An agreement of 80% or more of the voters was considered a consensus. If total agreement was not achieved on the first vote, the arguments and counterarguments were presented to reduce the disagreement, and a new vote was taken.

After this, an electronic survey was applied using Google Docs, with Likert-type agreement response options (1- Totally disagree, 2- Disagree, 3- Neutral, 4- Agree and 5- Totally agree). The Likert scale helped evaluate the degree of agreement in the group regarding the recommendations developed for each question.

The frequency of the votes was determined, and the mean and median were calculated with their 95% confidence intervals. Based on these results, the following actions were considered:

- Include the recommendation: If 80% voted between 4 and 5 or the median and its 95% CI was between 4 and 5.
- Do not include the recommendation: if 80% voted between 1 and 2 or the median and its 95% CI was between 1 and 2.
- Carry out a new discussion and round of voting: if an 80% vote was not reached in the rangea of 1 to 2 or 4 to 5.

For each question, the proportion of agreement on the proposed course of action was considered as a function of the number of votes/number of people surveyed.

Table 2 shows the results for each of the questions: the number of voters who marked one of the options from 1 to 5, as well as the calculated mean, median and 95% CI.

Following this, open questions were asked using an electronic form to gather expert opinion. The opinions were given independently and anonymously by each panel member (n = 15). All of the opinions were recorded in a matrix, providing a summary of the results obtained.

The strength of the recommendations was graded in two categories (strong and weak), following the recommendation of the Evidence to Decision framework, considering four domains that guided the assessment: the quality of the evidence, risk-benefit balance, use of resources, values and preferences of the healthcare professionals (feasibility – availability in the context, acceptability) and the opionions provided by the expert group.

1. Do the desirable effects of the recommendations outweigh the undesirable effects? (risk-benefit balance).
2. Could fewer healthcare resources be needed to implement the recommendations than to treat the health effects of not implementing them? (use of resources).
3. Is the inclusion of the recommendations in clinical practice acceptable to all the interested parties (patients, healthcare professionals and decision makers)? (acceptability).
4. Could the recommendations be implemented in all risk groups with few restrictions in the health-care system? (feasibility).

The response options for the expert opinion were:

- No
- Probably not
- Not sure
- Probably yes
- Yes
- It depends

The recommendations were deemed to be strong if the agreement was equal to or greater than 90%; otherwise, they were considered to be weak recommendations (Table 3).

The strong recommendations convey the message that the intervention should be offered to all or almost all patients, if in favor of the intervention (according to which, the desirable effects probably outweigh the undesirable effects), or that it should not be used in any or hardly any patients, if against the intervention (the undesirable effects are probably greater than the desirable effects). On the other hand, a weak recommendation conveys the message that what is being proposed should be considered in light of the clinical circumstances, preferences and values of each patient (Annex 3).

A strong recommendation was established when the clinicians considered that the advocated behavior should be implemented in most patients. When the recommendation is weak, it is recognized that the individual patient's preferences and values must be considered more carefully. Since these recommendations are based on a population perspective, the limited use of healthcare resources, acceptability and feasibility were considered in the expert opinions (Annex 3).

Questions and recommendations

Diagnostic approach

Question 1. How is HS-CHD defined?

Hemodynamically significant congenital heart disease related to RSV has been defined as uncorrected or palliated cyanotic CHD, or acyanotic CHD associated with documented pulmonary hypertension (pulmonary artery systolic pressure ≥ 40 mm Hg) and/or the need for daily medication to treat congestive heart failure[37].

Feltes et al.[21] conducted a multicenter, randomized, double-blind placebo-controlled trial with 1,287 children with CHD randomly assigned 1:1 to receive five monthly intramuscular injections of 15 mg/kg of palivizumab. This study was carried out in 76 centers in the United States (n = 47), Canada (n = 6), Sweden (n = 3), Germany (n = 4), Poland (n = 6), France (n = 4) and the United Kingdom (n = 6) and resulted in authorization for palivizumab use. Children with the following anatomic diagnoses were included in the cyanotic stratum: pulmonary atresia with ventricular septal defect, pulmonary atresia with intact ventricular septum, tetralogy of Fallot, single ventricle (which includes hypoplastic left or right heart), tricuspid atresia, double outlet right ventricle with transposition of the great arteries and Ebstein's anomaly or D transposition of the great arteries with/without ventricular septal defect, with/without pulmonary stenosis. The remaining diagnoses were stratified as acyanotic[21].

In a multicenter study which enrolled 747 patients in the study group and 809 in the control group from

Table 2. Percentage distribution of the agreement on the wording of the recommendations for each of the questions.

Recommendation	Votes n (%)					Mean	Median 95% CI
	1	2	3	4	5		
Recommendation 1	-	-	-	1 (0.07)	14 (0.93)	4.93	5.00 (4.80 a 5.06)
Recommendation 2	-	-	-	-	15 (100)	5.00	5.00
Recommendation 3	-	-	-	-	15 (100)	5.00	5.00
Recommendation 4.1	-	-	-	1 (0.07)	14 (0.93)	4.93	5.00 (4.80 a 5.06)
Recommendation 4.2	-	-	-	-	15 (100)	5.00	5.00
Recommendation 5	-	-	-	-	15 (100)	5.00	5.00
Recommendation 6	-	-	-	-	15 (100)	5.00	5.00
Recommendation 7	-	-	-	2 (0.13)	13 (0.87)	4.85	5.00 (4.68 a 5.03)
Recommendation 8.1	-	-	-	2 (0.13)	13 (0.87)	4.85	5.00 (4.68 a 5.03)
Recommendation 8.2	-	-	-	1 (0.07)	14 (0.93)	4.93	5.00 (4.80 a 5.06)
Recommendation 8.3	-	-	-	1 (0.07)	14 (0.93)	4.83	5.00 (4.57 a 5.09)
Recommendation 9	-	-	-	-	15 (100)	5.00	5.00
Recommendation 10	-	-	-	-	15 (100)	5.00	5.00
Recommendation 11	-	-	-	-	15 (100)	5.00	5.00
Recommendation 12	-	-	-	1 (0.07)	14 (0.93)	4.93	5.00 (4.80 a 5.06)
Recommendation 13	-	-	-	-	15 (100)	5.00	5.00

four of the largest pediatric cardiology centers in Taiwan, Chiu et al.[38] defined HS-CHD (according to the National Health Insurance [NHI] program's reimbursement criteria) as follows: cyanotic CHD prior to total correction (through surgery or transcatheter interventions) or after total correction but with residual cyanosis or heart failure symptoms; and acyanotic CHD with heart failure symptoms either before or after total correction. For the heart failure symptoms in these criteria, at least two of the following must be present: delayed growth with body weight under the third percentile, significant cardiomegaly (evaluated through imaging studies) and at least two anticongestive medications needed to control the heart failure[38].

In a prospective cohort study evaluating 217 children under the age of five hospitalized for acute respiratory infection at La Fundación Hospital Pediátrico de la Misericordia (HOMI) in Bogotá between August 2017 and June 2018, Lozano et al.[1] defined the criteria for CHD hemodynamic repercussions based on echocardiographic findings for ventricular and atrial septal defects, and included ventricular dysfunction, pulmonary hypertension, right chamber overload and dilation, the size of the heart defects, ventricular interdependence, ventricular septal displacement, geometric changes of the left ventricle and systolic dysfunction. Specifically for patent ductus arteriosus (PDA), the relationship between the left atrium and the aorta, the size of the defect, pulmonary over-circulation and systolic and diastolic left ventricular dysfunction were taken into account[1].

Through the surveillance system, Zhang et al.10 studied the detection and diagnosis of CHD in a total of 594,860 records during a follow up from 2018 to 2020 in Beijing. The diagnosis was based on the International Classification of Diseases, 10th version (ICD-10); simple CHD refers to single-defect heart disease that usually does not cause hemodynamic changes. Atrial septal defects ≥ 3 mm and PDAs ≥ 3 mm were included10. Twelve types of critical CHDs (CCHDs) were defined according to the United States Centers for Disease Control and Prevention standards, that is: coarctation of the aorta (CoA), double outflow right ventricle (DORV), Ebstein's anomaly, hypoplastic left heart syndrome (HLHS), interrupted aortic arch (IAA), pulmonary atresia, single ventricle (SV), tetralogy of Fallot (TOF), total anomalous pulmonary venous return (TAPVR),

Table 3. Overall percentage distribution of the consensus of expert opinion on each of the recommendations.

Recommendation	Vots n (%)						Strenght of recommendation
	No	Probably no	Not sure	Probably yes	Yes	It depends	
Recommendation 1	-	-	-	13.33	86.67	-	Weak
Recommendation 2	-	1.68	-	16.70	79.94	1.68	Weak
Recommendation 3	-	-	-	13.35	84.97	1.68	Weak
Recommendation 4.1	-	-	-	11.67	88.33	-	Weak
Recommendation 4.2	-	-	-	11.67	88.33	-	Weak
Recommendation 5	-	-	-	12.05	86.18	1.77	Weak
Recommendation 6	-	-	-	15.00	85.00	-	Weak
Recommendation 7	-	-	-	18.33	80.00	1.67	Weak
Recommendation 8.1	-	-	1.65	16.68	80.00	1.67	Weak
Recommendation 8.2	-	-	1.65	16.68	80.00	1.67	Weak
Recommendation 8.3	-	-	1.65	16.68	80.00	1.68	Weak
Recommendation 9	-	-	-	13.35	84.98	1.67	Weak
Recommendation 10	-	3.35	-	11.65	83.33	1.67	Weak
Recommendation 11	-	-	-	11.66	86.66	1.68	Weak
Recommendation 12	-	-	-	21.65	78.35	-	Weak
Recommendation 13	-	-	-	10.00	88.32	1.68	Weak

d-transposition of the great arteries (DTGA), tricuspid atresia and persistent truncus arteriosus (PTA)39. Critical CHDs include structural heart abnormalities that keep the heart from pumping blood normally to the body, leading to a high probability of low blood oxygen saturation[40]. The final diagnosis was based on echocardiography and was confirmed by pediatricians[10].

The definitions of CHD may not be consistent between studies. To facilitate the synthesis of information, we recorded the definitions of CHD used in the individual studies, which are useful and can be adopted to describe the epidemiology and management of CHD[7].

Recommendation 1

This consensus's group of experts suggests defining HS-CHD as follows:

1. Cyanotic CHD prior to intervention (palliative surgery, corrective surgery or hemodynamic intervention) or after intervention but with residual cyanosis or signs/symptoms of heart failure.
2. Acyanotic CHD with signs/symptoms of heart failure, either before or after total correction.

The presence of heart failure signs/symptoms was based on meeting at least two of the following three criteria: a) weight for height less than -2 SD; b) significant cardiomegaly on imaging studies; and c) and/or the need for medication to treat congestive heart failure.

Level of evidence	B
Strength of recommendation	Weakly in favor

Question 2. Who diagnoses CHD?

A good CHD prognosis is related to early detection and prompt referral to the specialist, with timely treatment and short and long-term follow up12. Interdisciplinary work taking into account all the different points of view with different approaches helps make more accurate diagnoses and determine a comprehensive approach. A route must be established from CHD diagnosis in the prenatal stage through birth and pediatric follow up[42].

For children with CHD, the pediatric primary care provider and pediatric cardiologist collaborate to identify the heart problem, control symptoms, advise on the necessary interventions and, finally, provide optimal transitions to adult providers. These children, who often have multiple comorbidities, receive better care through a team approach coordinated by the primary care physician[43].

Congenital heart disease has a multifactorial etiology, with environmental and genetic influences. Therefore, it is helpful for primary care providers, geneticists, obstetricians and pediatric cardiologists to have a basic understanding of these risk factors[43].

Various specialists play an important role in caring for patients with suspected or confirmed heart problems. Obstetricians, geneticists, maternal-fetal medicine physicians, fetal cardiologists, neonatologists, cardiovascular surgeons, pediatric interventional cardiologists, nurses, psychologists and social workers should work together to provide better care for the mother and fetus[42].

In its clinical guidelines for operable CHD in children under the age of 15, the Chilean Ministry of Health recommends that the CHD diagnosis be confirmed through echocardiography and clinical assessment by a cardiologist or pediatrician trained in cardiology (Grade of recommendation C[1])[44].

Ahmadi et al.[45] performed a case-control study including 898 children and their mothers who were referred to the Pediatric Cardiology Clinic at the School of Medicine of the Isfahan Medical Sciences University in Iran from 2014 to 2016. The objective was to better understand the risk factors for CHD, and they indicated that a strength in identifying the cases was that the diagnosis was confirmed by a pediatric cardiologist and documented through echocardiography.

Furthermore, in an observational cross-sectional study by Rehman et al.[46] in the pediatrics department of the Cardiology Institute of Peshawar, Pakistan (which included 123 patients, 101 [82.1%] of whom had acyanotic CHD and 22 [17.8%] cyanotic CHD), the diagnosis was confirmed with two-dimensional (2D) echocardiography and Doppler performed by a pediatric cardiologist.

The authors of the so-called overview of children with heart disease in Colombia, published in 2019[47,] recommended that "the Ministry of Health, subsidized and contributive regimen insurance companies, nurses, general primary care practitioners, obstetricians, pediatricians, pediatric cardiologists, pediatric cardiologists, and cardiovascular surgeons should coordinate to ensure comprehensive and timely management in providing appropriate heart disease care leading to quality of life and human dignity and total societal reintegration, with the same physical and cognitive development as any other child, which will result in better conditions for the child and society as a whole" [translation].

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[1] *Recommendation based exclusively on expert opinion or low-quality studies.*

Recommendation 2

The CHD diagnosis should be confirmed by a pediatric cardiologist.

Level of evidence D

Strength of recommendation Weakly in favor

Question 3. What are the necessary tools for diagnosing CHD?

Congenital heart defects entail long-term complications, including cardiac arrhythmias, infective endocarditis and pulmonary hypertension, as well as the probability of physical disability, abnormal neurodevelopment, cognitive and psychological disorders, and decreased ability to participate in children's normal activities[48].

The goal of CHD screening is to change its natural history by detecting it before symptoms appear and beginning early treatment, if necessary. If these diseases are diagnosed when symptoms are already present, the damage tends to be irreversible. The long-term outcomes improve if the disease is detected asymptomatically[48].

Prenatal diagnosis of severe CHD is associated with a better preoperative status, reduced morbidity (including neonatal hypoxemia), less need for invasive respiratory support, less metabolic acidosis and improved survival in selected defects[49].

If CHD is suspected prenatally, efforts should be made to determine its characteristics as well as whether it is an isolated defect or associated with another condition, either another malformation or a genetic disorder, or both. In this case, the steps to take include a detailed fetal echocardiogram, detailed morphological ultrasound and genetic assessment[50].

Prenatal diagnosis of this group of diseases is crucial for providing prompt treatment and improving the patients' prognosis[42]. While prenatal diagnosis is possible, a significant proportion of affected newborns are not detected. This "diagnostic gap," or the percentage of newborns with CHD undetected at hospital discharge, has been estimated at 25%[51,] leading to 700 to 100 child deaths attributed to delayed CHD diagnosis[40].

Intrauterine detection depends on several factors, and therefore it is essential for patients to have easy access to the healthcare system[50.] The prenatal detection rate varies widely depending on the country, the way in which this screening is carried out, the heart defect in question, the anatomical views routinely obtained and the sonographer's training[52]; thus, prenatal detection of CHD ranges from approximately 45 to 50% (95% CI: 33.5 - 57.0%). A meta-analysis and systematic review of seven cohort studies evaluating the rate of detection of heart diseases during prenatal screening concluded that prenatal detection was strongly correlated with the severity of the congenital defect, as the rate of detection of univentricular defects and heterotaxy was greater than 85%[53]. The rate of detection in screening programs can be improved by introducing clinical guidelines and protocols, along with a network to facilitate the referral of suspected patients to fetal cardiology experts, as well as setting up perinatal cardiology teams[54]. A well-organized detection program is essential for achieving a higher detection rate[53].

When the prenatal ultrasound test is used to detect or suspect CHD, this should lead to a detailed fetal echocardiogram with a very high precision for diagnosing CHD. This then allows the baby to be born and treated at an appropriate center[55].

Fetal echocardiography is the main tool for diagnosing and performing a detailed assessment of the fetal cardiovascular system[54]. The goals of fetal heart assessment include improving the understanding of fetal hemodynamics, predicting outcomes in utero, like fetal demise, identifying the requirements for a successful transition to the delivery room, including the need for postnatal interventions, and minimizing postnatal morbidity and mortality[56].

Fetal echocardiography includes two studies: fetal heart screening and advanced echocardiographic studies[42]. Finding a risk factor is an indication for advanced fetal echocardiography. Only 5 to 20% of fetuses with CHD have an identified risk factor for these defects. The remaining 80 to 95% of CHDs occur in people with no risk factors, in the low-risk population, and therefore it is essential to ensure effective fetal heart screening in the general population to maximize the detection of fetuses with heart disease[42]. A fetal echocardiogram is considered cost-effective when the risk of CHD is greater than 3%[43].

Sequential tests throughout pregnancy can predict the development of the disease in utero and during the transition to postnatal circulation at birth. This approach allows detailed prenatal counseling and enables planning to determine perinatal management, selecting fetuses with a risk of postnatal hemodynamic instability that could require a specialized birthing plan[49].

The Spanish Society of Neonatology recommends neonatal screening with pulse oximetry in the first hours after birth, together with prenatal detection and clinical assessment (Level of evidence A1)[57].

Prenatal diagnosis and the management of critical neonatal CHD have proven to play a significant role in optimizing the outcomes of newborns with

these problems, allowing prompt stabilization of the disease prior to heart surgery, and reducing the risk of perioperative morbidity, including the risk of perioperative neurological injury[49].

Postnatal screening for CHD is done through a physical exam, pulse oximetry and an echocardiogram[48].

In its 2013 clinical practice guidelines on the detection of congenital anomalies in newborns, the Colombian Ministry of Health and Social Security recommended universal pulse oximetry no sooner than 24 hours after birth as a screening strategy for CHD[48].

Pulse oximetry prior to discharge has an overall sensitivity of 76.3% (95% confidence interval [CI]: 69.5-82.0) and a specificity of 99.9% (95% CI: 99.7-99.9) for detecting CCHDs, with a false positive rate of 0.14% (95% CI: 0.07-0.22)58. The rate of false positives in detecting critical CCHDs was especially low when newborn pulse oximetry was performed more than 24 hours after birth rather than within the first 24 hours (0.06%; 95% CI: 0.03-0.13) vs. 0.42% (95% CI: 0.20-0.89); p = 0.027)[58]. This indicates that pulse oximetry is highly specific for detecting CCHDs, with moderate sensitivity, which meets the criteria for universal screening[59]. With an abnormal saturation, the probability of having CCHD is 5.5 times greater than when the result is normal[55].

Detecting CCHD using pulse oximetry in newborns prior to discharge improves the detection of CHD and is associated with reduced related child mortality[60]. Early detection of this type of condition benefits those who have it, reducing morbidity and mortality and improving their quality of life and life expectancy. Furthermore, it is advantageous for the Colombian healthcare system, as it is a simple, low-cost method that reduces the supplies used for treating and handling the mid- and long-term consequences of CCHD that is not diagnosed in time[61]. Prompt, appropriate intervention is associated with a more than 82% survival into adulthood, despite the surgical complications and long-term cardiac and non-cardiac comorbidities[62].

The evidence found suggests that pulse oximetry, along with the neonatal physical exam, has optimal operative characteristics, making it an appropriate screening test for detecting CCHD in newborns, which is essential in low and middle-resource settings where technological support is not always available[63]. This test is feasible and convenient, as it facilitates the newborn's transfer to a tertiary care hospital, reducing hospital stay and care costs[64].

Early postnatal CHD detection can be improved through standardized clinical exam protocols, but evaluating newborns with CHD requires clinical experience, due to the transition from fetal to postnatal circulation in newborns. In this context, some newborns with even lower hypoxemia due to delays in fetal circulation adaptation or those with primary lung disease, will inevitably have positive screening results; thus, immediate neonatal evaluation and the subsequent echocardiographic assessment will be crucial[65].

When CHD is suspected, echocardiography is the gold standard for diagnosis. However, it is not cost-effective nor feasible as a screening test in geographically large countries[55]. Almost all pediatricians agree with performing an echocardiogram on newborns with cardiorespiratory symptoms like cyanosis and tachypnea, or other non-cardiac abnormalities, to rule out CHD[66].

Diagnosing CCHD in early infancy depends on multi-view echocardiography, as a clinical CHD diagnosis based on a single view may be unreliable. Recent studies on the automated analysis of heart structure abnormalities tend to focus on two-dimensional single-view photographs or dynamic images from the echocardiogram[67].

A heart murmur is the most common reason for referring to a cardiologist and is the most frequent indication for an initial echocardiogram (61.1%), as opposed to other indications like chest pain (8.8%), syncope (5.2%), palpitations (2.1%) and fetal complications (0.1%). Furthermore, abnormal echocardiographic findings in the first year of life are more common in pediatric patients with heart murmurs68. Heart murmurs due to CHD are more easily auscultated once pulmonary vascular resistance decreases, which occurs after several weeks of life. Pathological murmurs which are described as stronger than 2/6, diastolic and holosystolic (pansystolic) and are associated with rubs, clicks or gallops are relevant for CHD, as this includes not only pathological murmurs but also asymptomatic non-syndromic murmurs[66].

In a systematic review by Yoon et al.66 which included six cohort studies, four cross-sectional studies and two case reports, for a total of 1,928 subjects from the United Kingdom (Newcastle upon Tyne), Israel (Jerusalem), Canada (Ontario/Ottawa), Canada (Quebec/Montreal), Turkey (Konya), Iran (Ardabil), United Kingdom (Birmingham), Jordan (Amman), United States (Florida/Miami), United States (Wisconsin/Madison), United States (New York) and Germany (Leipzig), the incidence of heart murmurs ranged from 0.6 to 8.6%. In addition, they found that more than 37% of newborns with asymptomatic non-syndromic heart murmurs had moderate to severe CHD, diagnosed through echocardiography. Therefore, this is a noninvasive tool which is useful for detecting heart problems

in newborns with heart murmurs and is a simple diagnostic procedure for CHD which improves the clinical outcomes of newborns with severe CHD.

Critical CHD often shows evident abnormalities on the echocardiogram, which can be easily recognized by physicians at primary care hospitals, allowing prompt referrals of patients to pediatric hospitals with specialists. However, due to the lack of experienced cardiac ultrasound operators, many children continue to have a delayed diagnosis of CCHD, especially the simple subtypes like atrial septal defects and ventricular septal defects, with a serious impact on their prognosis and future life[67].

In the "pediatric cardiology brigades" carried out in 11 Colombian departments from 2008 to 2013 by Fundación Cardioinfantil – Instituto de Cardiología to estimate the relative frequency, by departments and regions, of the various CHDs in children attending the brigades, an initial physical exam was conducted to detect the signs and symptoms of heart disease, along with pulse oximetry, vital signs, and a diagnostic electrocardiogram and echocardiogram. Through this strategy, 5,900 patients were evaluated; 56.1% (3,309) of the study population was diagnosed with CHD. Of all the CHDs, the five most common ones were: ventricular septal defect (15.6%), right ventricular stenosis or obstruction (9%), atrial septal defect (7.7%), patent ductus arteriosus (6.2%) and left ventricular outflow tract obstruction (5.3%)[12].

Cardiac screening should plan all the components; initially, training for the healthcare staff who will perform the test, parental awareness raising and provision of an efficient system for prompt referral to specialized healthcare centers to instate appropriate treatment according to the results obtained[64].

Recommendation 3

Congenital heart disease should be diagnosed through echocardiography performed by a pediatric cardiologist.

Level of evidence B

Strength of recommendation Weakly in favor

Good practice points

- Prenatal CHD screening should be done through fetal echocardiography.
- Postnatal CHD screening should be done with a physical exam and pulse oximetry prior to discharge.

Type of recommendation: Good practice recommendations from the clinical experience of the group developing the consensus. Represents the local contributions (CPGs).

Clinical management approach

Question 4.1 Should palivizumab be used for immunoprophylaxis against severe RSV disease in children with cyanotic CHD (any cyanotic disease)?

Question 4.2 Should palivizumab be used for immunoprophylaxis against severe RSV disease in children with uncorrected (noncyanotic) CHD or with partially corrected complex CHDs (palliative interventions) with hemodynamic repercussions (moderate or severe pulmonary hypertension, heart failure, hypoxemia)?

Question 4.3 Should palivizumab be used for immunoprophylaxis against severe RSV disease in patients with surgical correction and residual hemodynamically significant lesions and/or a history of severe pulmonary complications requiring prolonged mechanical ventilation?

There is no vaccine currently available to prevent RSV. The only prophylaxis against RSV disease is temporary passive protection with a preparation of monoclonal antibodies like palivizumab[69,70]. Palivizumab has only been studied in children under the age of two with underlying health problems. The efficacy of palivizumab prophylaxis (the risk of RSV-related hospital admissions) in mixed populations of infants at risk for severe RSV infection is associated with a 38 to 86% reduction in the risk of RSV-related hospital admissions, with a number needed to treat (NNT) of 2 to 24 to prevent a hospital admission[69]. Observational studies have shown wide variations in its effect and some studies have shown no benefit. Palivizumab has been used for more than two decades in many countries and has a good safety record, as cases of anaphylaxis, the most important serious adverse effect, are very rare[69].

A randomized, double blind, placebo-controlled study by Feltes, et al.[21] included 1,287 small children with HS-CHD from 76 centers, 682 (53.0%) of whom were in the cyanotic stratum and 605 (47.0%) in the "other" stratum, randomly assigned 1:1. Children were included if they were ≤ 24 months old at the time of randomization and had documented HS-CHD determined by the investigator and an unoperated or partially corrected CHD. Children were excluded if they had an unstable cardiac or respiratory status, including heart defects that were so severe that survival was not expected, or for which heart transplants were planned or expected; were hospitalized (unless discharge was expected within 21 days); were scheduled for heart surgery within two weeks of random assignment; required

mechanical ventilation, hemodynamic support with extracorporeal membrane oxygenation, continuous positive airway pressure or other mechanical support; or had associated noncardiac anomalies or end organ damage resulting in an expected survival of less than six months, or unstable end organ function abnormalities[21].

Children with the following anatomical diagnoses were included in the cyanotic stratum: pulmonary atresia with ventricular septal defect, pulmonary atresia with intact ventricular septum, tetralogy of Fallot, single ventricle including hypoplastic left or right heart, tricuspid atresia, double outlet right ventricle with transposition of the great arteries, and Ebstein's anomaly or D-transposition of the great arteries with/without ventricular septal defect, with/without pulmonary stenosis. The remaining children were stratified in the "other" (acyanotic) stratum[21].

The children were given an intramuscular injection of palivizumab (15 mg/kg) every 30 days for a total of five doses and were followed for 150 days. Overall, 93.0% of the palivizumab group and 91.8% of the placebo group received the five planned injections; 95.6% of the palivizumab group and 95.5% of the placebo group finished the study. Monthly palivizumab prophylaxis was associated with a 45% relative reduction in RSV hospitalizations (p = 0.003). The RSV hospitalization rates were 9.7% in the placebo group and 5.3% in the palivizumab group. The RSV hospitalization rates for infants less than six months old were 12.2% with placebo versus 6.0% with palivizumab, with corresponding rates of 7.3% versus 6.1% for infants 6 to 12 months old and 4.3% versus 1.8% for children 1 to 2 years old. In the cyanotic stratum, RSV hospitalizations decreased 29%, from 7.9% in the placebo group to 5.6% in the palivizumab group (p = 0.285). In the "other" stratum, RSV hospitalizations reduced by 58%, from 11.8% in the placebo group to 5.0% in the palivizumab group (p = 0.003). Children randomly assigned to palivizumab had significantly fewer total days of RSV hospitalization per 100 children (a 56% reduction, p = 0.003) and a 73% reduction in total RSV hospitalization days with increased supplementary oxygen per 100 children (p = 0.014). There was also a trend toward a lower number of days of intubation and ICU care in the groups treated with palivizumab[21].

Adverse events were similar between the treatment groups; the medication was not discontinued in any child due to a related adverse event. Serious adverse events occurred in 55.4% of those who received palivizumab and 63.1% of those who received placebo (p = 0.005). This tendency was found both in the cyanotic stratum (59.9 vs. 67.1%; p = 0.056) and in the "other" stratum (50.3 vs. 58.7%; p = 0.041).

The serious adverse events reported included arrhythmias in 0.2% of the palivizumab group and 0.3% of the placebo group and cyanosis in 3.6% and 2.2% of the cases, respectively. In the 30 days after the cyanotic heart disease, 14 patients in the palivizumab group (2.2%) and 12 patients in the placebo group (1.9%) underwent urgent or premature surgery or died (1 in each group). No serious adverse events related to palivizumab were reported. When the serious adverse events reported during all the RSV hospitalizations were removed from the analysis, the p value was 0.043. No deaths were attributed to the study drug[21].

These results showed the benefit of palivizumab prophylaxis in children with CHD. The reduction in RSV hospitalization rates occurred in both the cyanotic stratum (7.9% placebo vs. 5.6% palivizumab; p = 0.285) and the "other" or acyanotic stratum (11.8% vs. 5.0%; p = 0.003), although the reduction was only statistically significant in the acyanotic stratum. The study also showed that palivizumab is safe and well tolerated for severe RSV disease prophylaxis in this population[21]. The conclusion from this data is that monthly treatment with palivizumab offers a safe and effective means for reducing RSV morbidity and mortality in small children and infants with CHD[71].

The authors have clearly indicated that they found reductions in RSV hospitalization in both strata, although the study did not have sufficient statistical power for these subgroup analyses[21].

An observational study by Cohen et al.[72] gathered data on 19,548 subjects from 256 centers in the United States between 2000 and 2004 who received RSV prophylaxis with palivizumab, and evaluated the enrolled registry subjects with CHD during the four seasons. A total of 1,500 subjects with CHD were enrolled in this period (7.7% of the total registry cohort), 71% (n = 1,067) of whom had acyanotic CHD. Adherence to the injection program increased each season, from 72.0% in the first season to 85.3% in the fourth. Over the four seasons, 83.4% of the subjects with CHD adhered to the injection regimen. In the four registry seasons, follow up information was obtained including hospitalization data for 1,490 of the subjects with CHD[72].

Overall, 1.9% of the subjects with CHD treated with palivizumab prophylaxis were hospitalized for laboratory-confirmed RSV. The rate of hospitalization was significantly higher than the rate of hospitalization among registry subjects without heart disease (1.9% vs. 1.2%; p = 0.03). Among subjects with cyanotic and acyanotic CHD, the hospitalization rates were 2.6 and 1.6%, respectively. The subjects with cyanotic CHD had higher hospitalization rates than those with acyanotic CHD in three of the four seasons. A

decreasing trend was seen in the proportion of RSV hospitalizations in the four seasons (2002 to 2004) for all CHD cases (p = 0.0215) and for those with acyanotic CHD (p = 0.0046)[72].

The prospective data gathered in the registry of palivizumab results provide the largest available collection of published data on infants with CHD who have received palivizumab, and the results have shown low hospitalization rates that confirm the efficacy of this drug and are consistent with the clinical trial prior to approval and the AAP revised guidelines[72].

The multicenter study of 849 American and Canadian children under 24 months of age by Anderson et al.[73] used palivizumab in 434 (51%) of the eligible children hospitalized for lower respiratory tract infections, with RSV found in 403 (47%); the efficacy of palivizumab was 58% (95% CI: 43-69%). Likewise, this drug prevented intensive care unit admissions in 62% (95% CI: 35-78%). The unadjusted efficacy of palivizumab in preventing RSV-related hospitalizations in high-risk infants was 43.3% (95% CI: 34.1-51.2%). Among those with 29- to 35-week gestational age and ≤ 6-month chronological age without chronic pulmonary disease related to prematurity or CHD, the efficacy of palivizumab was 74% (95% CI: 56.2-84.7%). The study showed that palivizumab prevents RSV hospitalizations and intensive care unit admissions in high-risk infants, which suggests that real-life efficacy is similar to the efficacy found in the prospective clinical trials[73].

In a retrospective cohort study enrolling 101 children at the UCH Mostar Clinic of Childhood Diseases, Bosnia and Herzegovina, from October 2008 to March 2016, Raguz et al.[74] suggested that palivizumab is effective and efficient, as 25% of the children who were readmitted to the hospital did not have RSV. They concluded that palivizumab was effective and efficient in at-risk children during the eight-year immunization period with the five recommended doses. In addition, given the lack of etiological treatment of RSV infections, palivizumab is one of the potential preventive measures and represents an effective way of combating the virus, which is a cause of death in at-risk children, especially in developing countries[74].

Chiu et al.[38] conducted a multicenter observational cohort study of patients under one year old, with a cohort of 1,556 Taiwanese patients (747 patients in the study group and 809 in the control group), to analyze the efficacy of a new palivizumab protocol for HS-CHD in subtropical areas with no clear RSV season. Forty-three percent of the patients had cyanotic CHD, with a mean of 3.9 palivizumab doses per patient. They found that the RSV hospitalization rate was 49% (NNT 45) for all cases compared with the control group. The reduction in the RSV hospitalization rate was significant in cyanotic HS-CHD (65%; p = 0.028; NNT: 31), but not in acyanotic CHD (35%; p= 0.287). Days of hospitalization and the rate of admission to intensive care also decreased similarly in the treatment group (57 and 60%, respectively) compared to the control group. The hospitalization-free survival rate was significantly higher for those who received palivizumab prophylaxis (p = 0.009). The palivizumab prophylaxis protocol entailed six injection doses (15 mg/kg per dose) at a minimum of four-week intervals after diagnosing HS-CHD. The authors concluded that palivizumab prophylaxis with this monthly protocol for patients with HS-CHD is effective in reducing RSV-related hospitalizations. Likewise, the results suggest that palivizumab prophylaxis was effective in patients with cyanotic CHD and possibly in patients with acyanotic CHD[38].

Mohammed et al.[75] conducted a retrospective study of 530 patients who received palivizumab prophylaxis from October 2010 to March 2016 at King Abdulaziz Cardiac Center (KACC), in Riyadh, Saudi Arabia, with a little over half of the patients(52.5%) having hemodynamically significant acyanotic CHD. They found that, of those who received prophylaxis, 14 (2.6%) developed RSV infection, 13 (2.5%) had to be hospitalized and one (0.1%) had to be admitted to the ICU. The rate of RSV infection in the group receiving palivizumab was 3%. There were no serious side effects, although some patients reported a mild fever after the medication was administered. There were no RSV-related deaths; however, 11 patients died from causes unrelated to RSV infection. The average adherence rate for the six seasons was 97%. In conclusion, palivizumab is safe, well tolerated and effective as prophylaxis against severe RSV infection in patients with CHD, highlighting the reduction in hospital admissions[75]. The results of this study were consistent with those of international studies on palivizumab prophylaxis and Feltes et al.'s RCT[21].

Furthermore, in a prospective study by Chiu et al. of 772 patients born between 2014 and 2018 who received at least one dose of palivizumab at the Taiwan National University Hospital and were followed up to age two, 46% had cyanotic CHD and, of these, 23% had associated anomalies. The study's objective was to determine the RSV-related hospitalization rate in patients under the age of two with hemodynamically significant cyanotic and acyanotic CHD who received palivizumab prophylaxis according to the subtropical guidelines. The results showed a 5.5% RSV-related hospitalization rate at two years, 3.2% for patients 12 months old or younger, and 2.2% for patients 13 to 24 months old (p = 0.21). The hospitalization rates at

two years were similar for patients with cyanotic CHD (5.0%) versus acyanotic CHD (5.8%) (p = 0.64). Less than 10% of the RSV-related hospitalizations occurred in patients during the palivizumab prophylaxis period. Most infections occurred in patients (69%) who no longer met the criteria for palivizumab prophylaxis and in patients (17%) prior to beginning palivizumab prophylaxis because the CHD diagnosis was delayed. There were no significant differences in the ICU admission and endotracheal intubation rates for patients with acyanotic CHD versus cyanotic CHD. In addition, the study indicated that it was inexpensive to follow the subtropical guidelines, because the mean number of palivizumab injections was only 3.3 per patient. The authors concluded that the results support the claim that palivizumab prophylaxis reduces RSV-related hospitalization rates in children under one year of age who have HS-CHD[41]. Likewise, the results concur with the prophylactic effect of five palivizumab injections administered during the study by Feltes et al.[21].

A retrospective study by Ratti et al.[4] which enrolled 128 infants with HS-CHD in the pediatric cardiology division of a secondary care center in Italy concluded that there was evidence of palivizumab's efficacy in protecting patients under the age of two with HS-CHD against RSV disease and its potentially fatal complications. All patients with HS-CHD received RSV prophylaxis, with 26 only receiving partial prophylaxis (≤ 3 doses) because they were born at the beginning of the epidemic period and were diagnosed during the epidemic period or while hospitalized for bronchiolitis. Twenty-seven patients with HS-CHD had to be hospitalized for bronchiolitis and had a higher respiratory severity score than children in the control group (3.2 ± 0.9 and 2.3 ± 0.9, respectively); however, the difference was not statistically significant (p = 0.1211). Altogether, 28.6% of the analyzed patients with heart disease were admitted to the intensive care unit, compared to 10% in the control group[4].

Regarding the impact of palivizumab prophylaxis on hospitalization, 26 of the 27 patients with heart disease hospitalized for bronchiolitis did not receive a complete cycle of prophylaxis (≤ 3 doses). The multivariate analysis confirmed a significant association between the heart disease diagnosis, PICU and the length of hospital stay (p: < 0.0001 and 0.0036, respectively). Patients with CHD who completed a cycle of prophylaxis were less likely to be hospitalized for bronchiolitis (0.99 vs. 96.30%; p < 0.0001) compared to a group of healthy children of the same age. Patients with CHD with incomplete prophylaxis, besides being more likely to be hospitalized, if they were hospitalized, had a longer stay than the control patients (14.4 ± 21.7 days vs. 6.2 ± 2.3 days; p < 0.0001)[4].

In a postmarketing observational study (German Synagis™ Registry) in which data were recorded on the risk factors and clinical course of children who received at least one palivizumab injection between 2009 and 2016, Simon et al.[76] documented a total of 63,572 shots for the 12,729 evaluable patients from 2009 to 2016, with an average of 5.0 shots per patient per season. Hemodynamically significant CHD was the main reason for prophylaxis in 13% of all evaluable patients. The RSV hospitalization rate in the evaluable population with CHD was 0.8%, much lower than the hospitalization rate of 5.3% in the palivizumab group in the study by Feltes et al.[21]. A total of 16.9% required intensive care (median duration of three days), and 8.0% required mechanical ventilation. No RSV-related deaths were reported. Subject to the study's limitations due to its design and because the total number of patients with HS-CHD was lower than expected, this study confirms the efficacy and safety of palivizumab prophylaxis[76].

The recommendations published by AAP for the use of palivizumab in preventing RSV infections mention that decisions regarding palivizumab prophylaxis in children with CHD should be made based on the degree of physiological cardiovascular compromise. The children under 24 months of age with CHD who are most likely to benefit from immunoprophylaxis include: a) infants on medications to control congestive heart failure, b) infants with moderate to severe pulmonary hypertension, and c) infants with cyanotic heart disease[77]. An update in 2014 mentioned that certain children under the age of 12 months with HS-CHD could benefit from palivizumab prophylaxis, and the children who were most likely to benefit included infants with acyanotic heart disease who were receiving medications for congestive heart failure and would need heart surgery, as well as infants with moderate to severe pulmonary hypertension[22].

In 2010, the Sociedad Española de Cardiología Pediátrica y Cardiopatías Congénitas (SECPCC) [Spanish Society of Pediatric Cardiology and Congenital Heart Disease], using the modified Delphi method, proposed a series of recommendations for preventing RSV in children with CHD. Based on proven benefit and expert experience, palivizumab prophylaxis was considered to be advisable in:

a. Children under 24 months old with uncorrected CHD (cyanotic or acyanotic), or with partially corrected complex CHDs (palliative intervention), with hemodynamic repercussions (moderate-severe pulmonary hypertension, heart failure, hypoxemia).
b. Children with surgically corrected CHD who have residual lesions with hemodynamic repercussions.

c. Children with surgically corrected CHD with a history of serious pulmonary complications, who have required prolonged mechanical ventilation.

d. Children with corrected CHD without residual lesions but who continue to have hemodynamic repercussions immediately after surgery[78].

Regarding palivizumab prophylaxis against RSV infection, the Italian Society of Neonatology[79] indicates that it may be useful at the beginning of the epidemic season for children under 12 months old with HS-CHD who meet the following criteria:

a. Infants with cyanotic CHD prior to the surgical procedure or after a palliative procedure, as ordered by the pediatric cardiologist based on the patient's hemodynamic status (Level of evidence IV – Strength of recommendation A).

b. Infants with acyanotic CHD being treated for congestive heart failure who are scheduled for surgery (Level of evidence II – Strength of recommendation A).

c. Infants with moderate to severe pulmonary hypertension (Level of evidence II – Strength of recommendation A).

d. Babies with surgically repaired CHD who continue to need treatment for congestive heart failure (Level of evidence II – Strength of recommendation A).

In 2017, an international steering committee of physicians with experience in pediatric heart disease identified key questions about palivizumab administration and developed evidence-based recommendations using a quasi-Delphi consensus method. Based on the proven benefit and on clinical experience, immunoprophylaxis against severe RSV disease was recommended for:

a. Children under the age of two with unrepaired HS-CHD who require medication to control their congestive heart failure, are cyanotic (with oxygen saturation levels less than 85%), and have pulmonary hypertension or symptomatic respiratory tract anomalies (agree/disagree 7/1: Grade/level of evidence: 1A).

b. During the first year of life, for children with surgically treated HS-CHD with residual defects, or for children from one to two years old up to six months after surgery, or on a case-by-case basis (agree/disagree 8/0; Grade/level of evidence: 1A).

c. All children under two years old who are diagnosed or being treated (for example, with pulmonary vasodilators, oxygen, diuretics and anticoagulants) for idiopathic pulmonary artery hypertension, defined as a mean resting pulmonary artery pressure > 25 mmHg beyond the first months of life, or with CHD-related pulmonary hypertension or secondary to cardiomyopathy (agree/disagree 8/0; Grade/level of evidence: 1A; 1B).

d. Children under age two with a genetic or related condition who have HS-CHD, regardless of the primary diagnosis (agree/disagree 7/1; Grade/level of evidence: 2A)[80].

Routine RSV prophylaxis is not recommended in patients with non-hemodynamically significant CHD; for example, ostium secundum atrial septal defects/small ventricular septal defects, mild coarctation of the aorta, or small patent ductus arteriosus)[79,80].

In its consensus guidelines for the use of palivizumab in infants and children with CHD, the Japanese Society of Pediatric Cardiology and Cardiac Surgery (JSPCCS) recommends administering palivizumab at the beginning of the RSV season to prevent and minimize the incidence of RSV infection in children two years old or younger with CHD and at least one of the following problems: a) hemodynamically significant anomalies, b) have not undergone surgery or have residual symptoms after corrective or palliative surgery, c) pulmonary hypertension before or after surgery, d) scheduled (cardiac or noncardiac) surgery or heart catheterization, or e) mild hemodynamic abnormalities complicated by functional organic respiratory system abnormalities (Recommendation IA[2])[81].

A group of RSV experts from Europe, Canada and Israel, including representatives from the European Neonatal, Perinatal and Pediatric Scientific Societies[82], conducted a systematic review of the evidence for RSV prevention and palivizumab over the last five years, with the aim of developing prophylactic recommendations based on the fundamental principles for developed countries. Thus, they recommended palivizumab for: a) infants 12 months old or younger with hemodynamically significant cyanotic or acyanotic disease, and b) cyanotic or acyanotic children 12 to 24 months old who continue to be hemodynamically unstable (Level of evidence A, grade of recommendation A).

The National Advisory Committee on Immunization (NACI) makes recommendations for the Public Health Agency of Canada (PHAC)[69] and states that palivizumab should be offered at the beginning of the RSV season to infants under 12 months old who have HS-CHD (assessed by a pediatric cardiologist)

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[2] *Class I: Evidence and/or general agreement that a given procedure or treatment is beneficial, useful and effective. Level A: Data derived from multiple randomized clinical trials or a meta-analysis of these studies. Grade of recommendation A: Strong scientific basis, highly recommended.*

(Strong recommendation). Palivizumab may be considered in infants under 12 months old with chronic hemodynamically significant heart disease (assessed by a pediatric cardiologist) that is not congenital (Discretionary recommendation). Palivizumab may be considered at the beginning of the RSV season for children 12 to 24 months of age who are awaiting a heart transplant or who have received a heart transplant in the six months prior to the onset of the RSV season (Discretionary recommendation). Furthermore, the committee advises using the recommendations for chronic pulmonary disease for children with HS-CHD and chronic pulmonary disease (Strong recommendation).

Patients with heart disease should be individually assessed by their attending physicians, who have the key information to combine all the concurrent clinical and epidemiological circumstances in each case before making the best clinical decision for each patient's safety[78].

Palivizumab's efficacy in preventing severe RSV disease has been proven in several studies; therefore, it is recommended as passive immunization worldwide[83]. However, palivizumab's efficacy in preventing intensive care unit admissions is 62% (95% CI: 35-78%)[73], which is not satisfactory, considering its high cost. Palivizumab's efficacy must be maximized to reduce the cost of hospitalization, lost productivity and children's suffering[83]. The administration of this drug has been associated with a very low rate of serious adverse events[76].

Recommendation 4.1

The group of experts suggests the administration of palivizumab to prevent and minimize the incidence of RSV infection in children two years old or younger who have CHD and at least one of the following conditions:

a. Cyanotic CHD.
b. Hemodynamically significant acyanotic CHD.
c. Surgically or endovascularly treated CHD with residual lesions with persistent hemodynamic repercussions or cyanosis.
d. Severe pulmonary hypertension.

Level of evidence B

Strength of recommendation Weakly in favor

Recommendation 4.2

Routine RSV prophylaxis is not recommended in patients with CHD without hemodynamic repercussions (for example, ostium secundum atrial septal defects, small ventricular septal defects, pulmonary stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, or small patent ductus arteriosus).

Level of evidence D

Strength of recommendation Weakly against

Question 5. Should palivizumab be used as immunoprophylaxis to prevent severe RSV disease in children under the age of two being treated medically for cardiomyopathy?

Question 6. Should palivizumab be used as immunoprophylaxis to prevent severe RSV disease in children under the age of two with a heart transplant, during the first year after transplant?

Question 7. Should palivizumab be used as immunoprophylaxis to prevent severe RSV disease in children under the age of two with severe recurrent arrhythmias who have or have had hemodynamic repercussions?

Currently, there are no formal published recommendations for RSV immunoprophylaxis in infants with cardiomyopathy, although there is some evidence of the potential benefit in symptomatic children[80]. Despite this lack of formal guidance, the experts have indicated certain clinical guidelines.

The French Society of Pediatric Cardiology[84] recommends palivizumab prophylaxis in infants at high risk for respiratory complications after RSV infection, specifically in infants under one year old with cardiomyopathy with heart failure. Palivizumab prophylaxis decisions must be taken in collaboration with the pediatric cardiologist to optimize the cost-benefit ratio according to the degree of physiological cardiovascular compromise.

The Slovenian Association of Pediatrics Advisory Group for the Slovenian Ministry of Health[27] recommends the use of palivizumab in children under one year old with HS-CHD, pulmonary hypertension or cardiomyopathy.

In 2008, the Austrian Society of Child and Adolescent Health recommended the use of palivizumab in infants with hemodynamically significant heart defects (if corrective surgery is pending or a transplant is possible over a timespan of more than 24 months), pulmonary hypertension, or cardiomyopathy (excluding non-hemodynamically significant CHD)[27].

In 2010, the SECPCC[78], using the modified Delphi method, proposed a series of recommendations for preventing RSV in children with CHD, based on proven benefits and expert experience. Palivizumab prophylaxis was considered advisable for children under two years old with cardiomyopathy requiring medication. For mild cases not requiring medication, this indication was only for the first year of life. The

preventive use of palivizumab was also considered appropriate for children with heart disease scheduled for a diagnostic procedure (catheterization) or therapeutic procedure during the high-risk season, during the first two years of life, and for children with congenital or acquired immunodeficiency along with the CHD[78].

The 2009 AAP policy statement recommended palivizumab prophylaxis in: a) babies with mild cardiomyopathy who are not being medically treated for the condition; b) infants on medications to control congestive heart failure[77], and c) children under two years old undergoing heart transplantation during RSV season (2004)[22].

On the other hand, the Italian Society of Neonatology considered it useful to recommend palivizumab prophylaxis for children with HS-CHD, under the age of 12 months, at the beginning of the epidemic season and who meet the following criteria:

a. Babies with surgically repaired CHD who continue to require treatment for congestive heart failure (Level of evidence II – Strength of recommendation A).

b. Infants with congestive cardiomyopathy associated with heart failure who require anticongestive treatment (Level of evidence II – Strength of recommendation A).

c. Newborns on the heart transplant waiting list or in the post-transplant period (Level of evidence II – Strength of recommendation A)[79].

Based on the proven benefit and their own clinical experience, global experts[80] have recommended: a) RSV immunoprophylaxis in children under one year old with cardiomyopathy requiring medical treatment, including anticongestive treatment and oxygen support (Level of evidence: 2a; 2b[3]) and b) immunoprophylaxis against severe RSV disease for children under the age of two who are on the heart transplant waiting list, or in children under the age of two during their first year after heart transplantation, due to their immunosuppression (Level of evidence: 3).

The Czech Neonatology Society, Czech Pediatric Cardiology Society (for CHD) and the Czech Pediatric Pulmonology Society (for special populations)[27] recommend the use of palivizumab in infants with HS-CHD (with univentricular circulation or severe hypoxemia or with heart failure - significant left-right shunt for which surgery is indicated or dilated cardiomyopathy or severe pulmonary hypertension or following heart transplantation).

The Swedish Medical Products Agency recommends the use of palivizumab in infants with HS-CHD, pulmonary hypertension and cardiomyopathy (Exclusion: CHD which has been corrected or does not require surgery)[27].

The Hellenic Neonatal Society recommends the use of palivizumab in infants 12 months old or younger with hypertrophic cardiomyopathy (HCM) and HS-CHD at the beginning of the RSV season (infants with acyanotic CHD being treated for congestive heart failure and scheduled for surgery); in infants 12 months old or younger with HCM and moderate to severe pulmonary hypertension at the beginning of the epidemic season; and in infants 12 months old or younger with HCM and congestive heart failure being treated at the beginning of the epidemic season[27].

The Italian Society of Neonatology recommends the use of palivizumab in infants with HS-CHD awaiting corrective surgery or transplantation, pulmonary hypertension and cardiomyopathy[27].

The Turkish Neonatal Society recommends the use of palivizumab prophylaxis for children under the age of two with CHD and cardiomyopathy with hemodynamic involvement who require medication, and for those under 12 months old with repaired CHD who still need medication, as well as for patients on the transplant list or in the post-transplant period[27].

The JSPCCS consensus guidelines for the use of palivizumab in infants and children with CHD recommend administering palivizumab to prevent and minimize the incidence of RSV infection in children 24 months old or younger at the beginning of the RSV season and the onset of cardiomyopathy, idiopathic pulmonary arterial hypertension, arrhythmias, etc. (including those awaiting heart transplantation or those in the early phase after transplant) who have hemodynamically significant anomalies (Recommendation IIA, level of evidence C)[81].

The NACI (2022) has recommended that the PHAC offer palivizumab to children 12 to 24 months old who are awaiting a heart transplant or receive a heart transplant in the six months after the RSV season begins (Discretionary recommendation of the Canadian NACI). The Canadian NACI concludes that

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3 II: evidence obtained from an individual appropriately designed randomized study.
A: indicates a particular recommendation supported by good quality scientific evidence.
B: there is some doubt that the procedure/intervention should always be recommended, but its implementation should be carefully considered.
Class IIa: The weight of the evidence/opinion is in favor of its usefulness/efficacy.
Level C: expert consensus opinion based on clinical experience and/or small-scale clinical studies, including retrospective studies and registry-based studies.

there is insufficient evidence to recommend the use of palivizumab in this population (Grade I evidence); therefore, this is based on expert opinion. There is no evidence on the burden of RSV disease or the use of palivizumab in this group. It is postulated that these infants will have severe cardiac dysfunction and will probably receive immunosuppresant therapy during the RSV season and may benefit from palivizumab[69].

Hayes et al.[85] performed a retrospective cohort study using the Pediatric Health Information System (PHIS) database which included 3,815 pediatric patients hospitalized for transplantation at Nationwide Children's Hospital, Columbus, Ohio. This study found that one out of six pediatric solid organ transplant recipients was hospitalized for RSV or a vaccine preventable illness (R/VPI) in the first five years after transplant, and that heart transplant recipients had a higher risk of hospitalization than other solid organ transplant recipients.

The universe of this study was all orthotopic heart transplant recipients under the age of 18 who underwent heart transplantation between September 2003 and December 2018 and were available in the PHIS database. Out of 3,815 transplant recipients, 17.9% had an R/VPI hospitalization during the study period. The patients with more than one R/VPI-related hospitalization were younger at the time of transplant and more prone to having an underlying CHD or to undergo another transplant during the study period. In the adjusted analyses, there was a greater risk of R/VPI hospitalization in patients who required mechanical circulatory support prior to transplant, patients who were induced with ≥ 2 immunosuppressants and patients under the age of two in the first year after transplant. Children under age two were found to have a higher risk of R/VPI in the first year after transplant. It should be noted that the reason for transplant (CHD vis-à-vis cardiomyopathy) was not significant, which indicates that the higher incidence of R/VPI in patients with CHD was probably due to their age at transplant[85].

Recommendation 5

Palivizumab administration is suggested to prevent and minimize the incidence of RSV infection in children 24 months old or younger with HS-CHD.

Level of evidence	D
Strength of recommendation	Weakly in favor

Recommendation 6

Immunoprophylaxis against severe RSV disease should be considered in children under the age of two who are on the waiting list for heart transplantation, and during the first year after heart transplantation, due to their immunosuppressed state.

Level of evidence	C
Strength of recommendation	Weakly in favor

Recommendation 7

Immunoprophylaxis with palivizumab is suggested in children under the age of two with tachycardiomyopathy. This recommendation is based on expert opinion.

Level of evidence	B
Strength of recommendation	Weakly in favor

Approach to pharmacological management

Question 8. When and how should RSV prophylaxis be resumed in patients with heart disease in whom it was suspended due to a surgical intervention with extracorporeal circulation?

Since a 58% mean reduction in the serum concentration of palivizumab has been found after surgical procedures involving extracorporeal circulation[21], for children who still need prophylaxis after a surgical procedure, a postoperative palivizumab dose (15 mg/kg) should be considered for children under the age of 24 months after surgery with extracorporeal circulation as soon as they are hemodynamically stable (IA)[22,77].

Hospitalized infants who qualify for prophylaxis during the RSV season should receive the first dose of palivizumab 48 to 72 hours before discharge or immediately after discharge (CIII)[77].

The SECPCC recommended that palivizumab prophylaxis (15 mg/kg of body weight in an intramuscular injection) in children with heart disease who meet the criteria should begin the month before the beginning of the epidemic season and should continue monthly until the entire season has passed. Patients with heart disease who receive RSV prophylaxis and undergo a surgical procedure with extracorporeal circulation should receive an additional dose after the intervention, as soon as they are clinically stable[78].

Global experts[80] recommend immunoprophylaxis against severe RSV disease during the first year of life for children with surgically corrected HS-CHD with residual defects, or for children 1 to 2 years old, up to six months after surgery, or on a case-by-case basis. The administration of one dose of palivizumab should be considered immediately after surgeries entailing extracorporeal circulation, due to the reduction in serum levels to nonprotective levels (Level of evidence 1a, 1b).

For children with HS-CHD after surgery, Dr. Eun Jung Bae, in Germany, continues treatment for six months, even after the hemodynamic defect has been resolved, to allow time for recovery[80].

For children with palliated CHD, Jung Bae continues treatment for six months after palliative surgery and preferably for the first two years of life[80].

Dr. Juan M. Gil-Jaurena, in Mexico, considers RSV immunoprophylaxis for children with heart disease who are scheduled for a diagnostic procedure (like catheterization) during the RSV season, or who are at risk during the first two years of life[80].

Dr. Ali Dodge-Khatami, in the United Arab Emirates, uses case-by-case clinical judgement for patients with HS-CHD or partially corrected CHD and recommends RSV immunoprophylaxis during the rest of the season or for two months, whichever is longer, to allow maximal recovery from surgery[80].

For children one to two years old who have undergone early surgical intervention for CHD, RSV immunoprophylaxis was also recommended up to six months after surgery or on a case-by-case basis. However, there were some differences of opinion regarding how long immunoprophylaxis should continue after surgery. Personalized decisions may be needed and may depend on the purpose and outcome of the surgical intervention; that is, if the surgery is palliative, there may be general agreement for prophylaxis during at least the length of the RSV season. For cases with complete surgical correction, the immunoprophylaxis decisions may seem less clear; however, ongoing prophylaxis may be appropriate for all children with CHD who undergo surgery, both palliative as well as completely corrective, to allow enough time for general recovery and physiological remodeling. Furthermore, since the serum concentration of palivizumab has been found to decrease more than 50% (that is, to non-protective levels) after cardiopulmonary bypass, the administration of a dose of palivizumab should be considered after this type of surgery to completely protect patients from the risk of severe RSV disease during the vulnerable recovery period[80].

Children with cyanotic CHD have a higher risk of RSV-associated hospitalization than those with acyanotic CHD. Children with cyanotic CHD are discharged from the hospital after palliative surgery and continue their everyday life at home and in their community. Hypoxia and high carbon dioxide caused by RSV infection can easily alter their hemodynamics by affecting pulmonary and systemic vascular resistance. Therefore, children with cyanotic CHD are a priority target for palivizumab administration[83].

Recommendation 8.1

For children under 24 months of age who still need prophylaxis after a surgical procedure, a postoperative dose of palivizumab (15 mg/kg) is recommended after undergoing extracorporeal circulation.

Level of evidence C

Strength of recommendation Weakly in favor

Recommendation 8.2

The experts suggest that immunoprophylaxis be administered after the intervention, when the patient is clinically stable, meaning that a postoperative safety period has passed and the patient is not in intensive care, does not require inotropic therapy and is in the process of hospital discharge.

Level of evidence D

Strength of recommendation Weakly in favor

Recommendation 8.3

It is suggested that the decision to administer palivizumab after a surgical intervention be personalized by the attending physician (pediatric cardiologist, pediatrician, neonatologist, pediatric intensivist) according to the patient's clinical condition and surgical outcome, while the patient is hospitalized and expecting discharge.

Level of evidence C

Strength of recommendation Weakly in favor

Question 9. Is there any indication for an adjustment to the five palivizumab doses for patients with heart disease in countries without seasons?

Palivizumab is an IgG1 humanized monoclonal antibody that specifically targets the RSV fusion protein and is very active against RSV-A and -B strains. This medication (15 mg/kg intramuscularly) has proven to be safe, well tolerated and effective for preventing severe RSV disease in high-risk pediatric patients[86]. A monthly injection is needed to provide adequate protection against RSV infection[21].

The AAP[77] has recommended a monthly palivizumab injection for all infants with HS-CHD for a maximum of five doses during the prevailing RSV season, regardless of the month in which the first dose is applied, for all geographical locations.

Due to seasonal clustering, AAP[77] does not recommend administering more than five monthly doses within the United States, as five monthly doses of palivizumab at 15 mg/kg per dose provide

more than six months (> 24 weeks) of serum concentrations of palivizumab above the desired level for most children. For qualified babies who need five doses, a dose beginning in November and continuing for a total of five monthly doses will provide protection for most until April, and this is recommended for most areas in the United States. If prophylaxis begins in October, the fifth and final dose should be administered in February, which will provide protection for most babies until March. If prophylaxis begins in December, the fifth and final dose should be administered in April, which will protect most babies until May[22].

In subtropical countries and equatorial regions like Taiwan and Southeast Asia, the seasonal clustering of RSV infection is not evident[38]. Although monthly palivizumab administration for prophylaxis against RSV infection in high-risk infants has proven to be effective, it should be scheduled according to the local circulation patterns of the virus[87].

Claydon et al.[88] performed a descriptive cohort analysis based on a population of 406 approved courses of palivizumab over four seasons (2012/13 to 2015/16) in 325 children with HS-CHD enrolled in the RSV immunoprophylaxis program in British Columbia, the only jurisdiction that uses abbreviated schedules with four doses and a set date. The children received up to four 15 mg/kg doses intramuscularly; the second dose was administered 21 days (a maximum of 28 days) after the first dose, and the subsequent doses were administered 28 days (a maximum of 35 days) apart. If a baby underwent extracorporeal circulation during the season, an additional dose was administered (immediately after the procedure). Of the 391 palivizumab courses administered, 351 (89.8%) included up to four doses and 38 (9.7%) included an additional fifth dose, which was received immediately after heart bypass surgery in 33 cases (8.4%) and at the physician's discretion in 5 cases (1.3%). Two courses (0.5%) included six doses, at the physician's discretion. Another 30 courses (7.7%) were not completed, 7 due to noncompliance during the season, 3 due to hospital admission, 4 due to the patient's death, 2 at the physician's discretion and 14 due to unspecified causes. Twenty-four (96%) of the 25 admissions occurred within the dosing period of four palivizumab doses, and the other one occurred 52 days after the fourth dose. Sixty-four (72%) of 89 admissions were RSV negative. In 17 admissions, the patient had a positive RSV test, with a rate of confirmed RSV admissions of 4.2 per 100 season approvals (95% CI: 2.5-6.6%). This result is consistent with the fact that most RSV infections in North America and Europe occur in December and January, when palivizumab coverage is not expected to differ between four and five dose schedules. In infants with HS-CHD, a set-date four-dose palivizumab program during a six-month season provided seasonal protection comparable to that of a clinical trial with a standard five-dose program[88].

In a retrospective observational study enrolling 498 patients (n = 277 for CHD), Kamori et al.[83] evaluated the relationship between the timing of the first dose of palivizumab and its effect on real-world RSV-associated hospitalization. A chart review was performed from 2015 to 2019. Twenty-one percent (105) received the first dose in July, when the RSV season in Japan tends to start. According to the indications for palivizumab administration in the Japanese health insurance system, children (≤ 2 years old) with HS-CHD were included. Those with an indication for palivizumab were included beginning on July 1 each year. Palivizumab prophylaxis was stopped in the middle of March each year, when, according to the investigators, the season had finished. The number of patients by total number of doses was: 2 for 4 times, 17 for 5 times, 47 for 6 times, 163 for 7 times, 265 for 8 times and 4 for 9 times. Twenty-three patients (4.6%, 23/498) were hospitalized for RSV infections during the follow up period, 18 of whom had CHD. The study found that patients were hospitalized for RSV infection prior to palivizumab administration or after a single dose in the first stages of the RSV season, and that cyanosis caused by CHD was a significant risk factor (3.25; 95% CI: 1.33-7.94; p< 0.01) for RSV hospitalization in patients with an indication for palivizumab prophylaxis. Delays in administering this medication at the beginning of the season increase the rate of RSV hospitalization[83].

The finding of a low RSV hospitalization rate once the rate of administration reached 100% suggests that early administration of the first dose is essential. However, identifying the beginning of the RSV season is a challenge. Difficulties in access to medical care and the lack of human and non-human resources in hospitals must be overcome to administer palivizumab as early as possible. Furthermore, it is tricky to determine the beginning of the season as it can vary from year to year, which makes it hard to begin administration at the right time. A realistic approach is that children with risk factors should begin palivizumab administration as soon as possible after a sign that the RSV season has begun, to avoid virus-related hospitalizations[83].

Recommendation 9

Administer a maximum of five 15 mg/kg doses of palivizumab to all children under the age of 24 months with HS-CHD once the diagnosis is confirmed, with a 28-day interval between doses.

Level of evidence	B
Strength of recommendation	Weakly in favor

Question 10. What is recommended for patients with heart disease when they are hospitalized and are receiving RSV prophylaxis with palivizumab?

The AAP[77] recommends that infants who have begun palivizumab prophylaxis at the onset of the season and are hospitalized on the date they were to receive the next monthly dose should receive this dose as scheduled as long as they remain hospitalized (level of evidence IA).

The JSPCCS consensus[81] recommends that when palivizumab is administered to infants or small children discharged from the neonatal intensive care unit/intensive care unit, the dose be administered at least three days prior to discharge, considering the time needed to raise the serum concentration of the medication. An effective concentration of palivizumab is maintained for a shorter period of time after the first dose than after the second; therefore, a shorter interval is recommended between the first dose and the next dose after discharge[81].

Recommendation 10

Infants who have begun palivizumab prophylaxis and are hospitalized for something unrelated to RSV should not interrupt their palivizumab immunoprophylaxis schedule as established prior to hospitalization.

Level of evidence D

Strength of recommendation Weakly in favor

Question 11. What is recommended for patients with heart disease when they are hospitalized and have not yet received RSV prophylaxis with palivizumab?

The NACI indicates that palivizumab should not be administered to prevent nosocomial RSV in eligible children who remain hospitalized. It may be considered when all other measures to control an RSV outbreak in a neonatal intensive care unit have failed[69].

The guidelines for palivizumab prophylaxis in infants and small children at higher risk of RSV infection in Saudi Arabia[89] do not recommend palivizumab prophylaxis to prevent healthcare-related RSV disease.

Recommendation 11

The panel of experts suggests that heart disease patients who are hospitalized and meet the inclusion criteria should begin their palivizumab immunoprophylaxis schedule during their hospital stay or ensure that it is administered immediately after discharge.

The panel of experts drafted the recommendation seeking to encourage the adherence and protection of hospitalized patients, considering that palivizumab immunoprophylaxis should be started seven days prior to hospital discharge, according to the eligibility criteria established for patients at risk for RSV.

Level of evidence D

Strength of recommendation Weakly in favor

Question 12. How and when should palivizumab prophylaxis continue in patients with heart disease who are infected with RSV?

The "Diagnosis and Management of Bronchiolitis" clinical practice guideline published by AAP in 2014 does not recommend continuing monthly prophylaxis for infants or small children who are hospitalized for RSV[90].

Respiratory syncytial virus is classified into subgroups A and B, based on antigenic differences in surface glycoprotein G. The subgroups are classified further into genotypes according to the genetic analysis. The ability of RSV to cause reinfections throughout life is probably due to both strain variability as well as an immune response that does not completely protect against subsequent infections. Reinfections occur with both heterologous and homologous strains. More than one RSV strain may circulate simultaneously in a community. However, repeated hospitalizations for RSV during a single season are rare[22]. Due to the rarity of repeat infections in the same season, the AAP recommends stopping palivizumab prophylaxis in children who are hospitalized for RSV. This is confirmed by the Canadian NACI[69] when it states that palivizumab should be discontinued for the season if a child is hospitalized for an RSV infection.

Furthermore, the Canadian Paediatric Society Infectious Diseases and Immunization Committee[91] does not recommend continuing monthly palivizumab for children hospitalized for an RSV infection. Repeated RSV infections in a single season are rare. Although it is recommended in the product's monograph, the number needed to treat is, undoubtedly, very high if palivizumab is continued after an RSV infection[92].

The clinical practice statement developed by the Ministry of Health with support from the National Immunization Technical Advisory Group (NITAG) in Saudi Arabia[89] recommends suspending monthly prophylaxis in any child hospitalized for RSV.

The JSPCCS[81] recommends that, when patients have an RSV infection while receiving palivizumab injections, they should continue to be administered throughout the RSV season to prevent serious lower respiratory tract infections due to reinfection.

The Saudi Pediatric Pulmonology Association[93] recommends that, if an infant receiving RSV prophylaxis experiences a breakthrough of the virus, monthly prophylaxis should continue as planned until a maximum of five doses have been administered (Recommendation 3B).

Recommendation 12

Suspend palivizumab immunoprophylaxis in children under the age of 24 months with CHD who are hospitalized for an RSV infection.

Level of evidence D

Strength of recommendation Weakly in favor

Good clinical practice focus

Question 13. Are palivizumab prophylaxis programs advisable?

In a prospective observational cohort study that enrolled 104 children two years old or younger with confirmed HS-CHD who underwent palivizumab immunoprophylaxis from January 1 to June 31, 2016 at a specialized cardiology referral hospital in Belém, Pará, Brazil, de Souza et al.[5] evaluated the efficacy of the palivizumab program and its recommended monthly doses in these children. The results showed that there was not a single human RSV-positive case after palivizumab immunization, which suggests total efficacy of immunoprophylaxis with this medication. However, its effectiveness cannot be established, as there was no control group of similar patients who did not receive passive immunization with palivizumab[5].

In a retrospective cohort study with a sample of 129 children recruited at Hospital Materno-Infantil Presidente Vargas (HMIPV) and Hospital de Clínicas de Porto Alegre (HCPA), both located in the city of Porto Alegre, in the south of Brazil, Batista et al.[94] evaluated the effectiveness of a public palivizumab prophylaxis program on the incidence of hospitalizations for lower respiratory tract infections and RSV in children at high risk for severe RSV infections. The sample included children under the age of two with HS-CHD. The cases (palivizumab group) were selected between May 2014 and August 2016, after the inclusion of palivizumab in the Brazilian public health system (SUS), and the controls were selected between May 2009 and August 2016. Altogether, 53.5% (n = 69) received palivizumab, with 78% receiving three or more doses. On the other hand, 60 children (46.5%) did not receive palivizumab. The use of palivizumab remained independently associated with all-cause hospitalization and lower respiratory tract infection hospitalization and was a protective factor, with 66 and 52% reductions in the relative risk, respectively. The results suggest that the adoption of the prophylactic program achieved the expected effectiveness for the study patients, which corroborates the findings of previously published international clinical trials.

In a retrospective study of 222 patients with HS-CHD in Hong Kong, Chen et al.[95] evaluated the proportion of infants who could have benefited from a palivizumab prophylaxis program, indicating that, considering the efficacy of palivizumab, the NNT to prevent human RSV with a five-dose regimen would be 55.6 (95% CI: 66.6-74.6), while for a six-dose regimen it would be 38.5 (95% CI: 33.3-43.4). They showed that the human RSV burden in patients with HS-CHD in Hong Kong, a subtropical region, is at least as high, if not higher, than in countries with a temperate climate.

In a controlled, interrupted time series evaluating the effectiveness of two palivizumab programs targeting high-risk infants occurring before the children's second birthday and using the demographic and health administrative databases available for all children born in Ontario, Canada from 1993-2016, Fitzpatrick et al.96 stated that the rates of severe RSV-related diseases substantially decreased in high-risk infants once palivizumab was introduced in Ontario in 1998. Immediately after the introduction of palivizumab in 1998, the "level change" among children eligible for palivizumab was -18.3% (-46.6 to 9.9), while the "level change" in children ineligible for palivizumab was -7.9% (-14.7 to 1.2), resulting in a relative "level change" of -10.4 (-39.4 to 18.6) among infants eligible for palivizumab compared to ineligible infants. Relative to the changes in ineligible infants, the improvement in RSV rates seen after the first introduction of palivizumab in the eligible infants was not statistically significant.

Among infants under six months old who were eligible for palivizumab, the absolute rate reduction during the study period was 65.4% (51.4 to 75.4%). On the other hand, a 31.1% reduction (26.0 to 36.0%) was found in ineligible infants under six months of age. The reduction in RSV admissions in infants eligible for palivizumab was clinically significant but not statistically significant compared to ineligible infants, which suggests reduced effectiveness compared with the clinical efficacy[96].

The reduction in severe RSV among children who were ineligible for palivizumab could reflect changes in RSV dynamics, the prevalence of cofactors affecting the severity of the infection (for example, parental smoking) or other factors. This large population-based study spanning several decades found that severe RSV-related diseases decreased substantially among high-risk infants in Ontario, Canada[96].

Although there is a lot of evidence supporting the clinical efficacy of palivizumab, this paper provides essential information on the real-world effectiveness

of palivizumab programs, which appear to have reduced their effectiveness compared with the clinical trial estimates. Further research is needed to determine if, and to what extent, the effectiveness of palivizumab programs could be improved by ensuring that therapeutic levels are maintained throughout the entire RSV season (that is, adhering to the monthly dosing program) and that efforts are made to promote the availability and acceptance of palivizumab among eligible children, especially when they are publicly funded[96].

Considering the multitude of steps needed to receive a complete palivizumab series (for example, parental knowledge, eligibility, administration, approval and adherence), efficacy studies are essential for determining its real-world impact. Even in clearly eligible high-risk infants, the real efficacy of these palivizumab programs does not compare to the trial-based efficacy estimates[96].

Including the RSV immunoprophylaxis doses in the regular immunization program can help mitigate RSV-related mortality. However, a more detailed review of the benefits and feasibility of this recommendation is needed[93].

Recommendation 13

Implementation of and adherence to palivizumab immunoprophylaxis is recommended for patients with CHD who meet the inclusion criteria, through formal, organized programs that allow greater coverage and resource optimization.

Level of evidence	D
Strength of recommendation	Weakly in favor

Users

- Healthcare teams providing direct patient care (primary care physicians, specialists and other healthcare staff) and involved in patient diagnosis and treatment.
- Administrative decision makers: Health insurance companies, healthcare centers, local authorities and the Ministry of Health and Social Security.
- Academia.
- Patients' families and caregivers.

Statement of conflicts of interest

All members of the development group and experts participating in this consensus provided a statement of conflicts of interest at the beginning of the process, prior to the formal consensus sessions, and none have a conflict of interest related to the drafting of this document.

Editorial independence

The technical work for developing this document has been conducted independently by the development group. It should be clarified that neither the research company that supported the development of the document nor the pharmaceutical company that sponsored the project have rights to the document.

The project followed the ethical principles for research in Colombia established in Resolution 8430 of 1993.

Funding

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Annexes

Annex 1. Search terms.

Antiviral agents/*administration & dosage
Congenital heart disease
Heart defects, congenital
Heart defects, congenital/*complications
Heart defects, congenital/diagnosis
Heart defects, congenital/diagnostic imaging
Hospitalization
Humans
Infant
Infant, newborn
Palivizumab
Palivizumab/*administration & dosage
Palivizumab/*therapeutic use
Patient compliance/*statistics & numerical data
Primary prevention/methods
Respiratory syncytial virus
Respiratory syncytial virus infections/*prevention & control
Respiratory syncytial viruses
Respiratory tract infections/*prevention & control/virology

Palivizumab/*therapeutic use
Patient compliance/*statistics & numerical data
Primary prevention/methods
Respiratory syncytial virus
Respiratory syncytial virus infections/*prevention & control
Respiratory syncytial viruses
Respiratory tract infections/*prevention & control/virology

Annex 2. Search algorithms

Date of search	Data source	Study design	Search algorithm	Results
7/10/2022	PubMed	All	(("palivizumab"[MeSH Terms] OR "palivizumab"[All Fields]) AND ("respiratory syncytial virus infections"[MeSH Terms] OR ("respiratory"[All Fields] AND "syncytial"[All Fields] AND "virus"[All Fields] AND "infections"[All Fields]) OR "respiratory syncytial virus infections"[All Fields]) AND ("controlling"[All Fields] OR "controllability"[All Fields] OR "controllable"[All Fields] OR "controllably"[All Fields] OR "controller"[All Fields] OR "controller s"[All Fields] OR "controllers"[All Fields] OR "controlling"[All Fields] OR "controls"[All Fields] OR "prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "control"[All Fields] OR "control groups"[MeSH Terms] OR ("control"[All Fields] AND "groups"[All Fields]) OR "control groups"[All Fields]) AND ("heart diseases"[MeSH Terms] OR ("heart"[All Fields] AND "diseases"[All Fields]) OR "heart diseases"[All Fields] OR ("heart"[All Fields] AND "disease"[All Fields]) OR "heart disease"[All Fields])) AND (y_5[Filter])	36
7/10/2022	PubMed	All	(((("palivizumab administration"[All Fields] AND ("dosage"[All Fields] OR "dosages"[All Fields])) OR "palivizumab/therapeutic use"[MeSH Terms]) AND ("heart defects, congenital"[MeSH Terms] OR ("Heart"[All Fields] AND "Defects"[All Fields] AND "Congenital"[All Fields]) OR "congenital heart defects"[All Fields] OR ("Congenital"[All Fields] AND "Heart"[All Fields] AND "disease"[All Fields]) OR "congenital heart disease"[All Fields])) OR "heart defects, congenital/complications"[MeSH Terms] OR ("respiratory syncytial viruses"[MeSH Terms] OR ("respiratory"[All Fields] AND "syncytial"[All Fields] AND "viruses"[All Fields]) OR "respiratory syncytial viruses"[All Fields])) AND ((y_5[Filter]) AND (clinicalstudy[Filter] OR clinicaltrial[Filter] OR comparativestudy[Filter] OR consensusdevelopmentconference[Filter] OR controlledclinicaltrial[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR practiceguideline[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))	920
7/10/2022	PubMed	All	(("palivizumab/therapeutic use"[MeSH Terms] AND "heart defects, congenital"[MeSH Terms] AND "respiratory syncytial viruses"[MeSH Terms]) OR "heart defects, congenital/complications"[MeSH Terms] OR "palivizumab"[MeSH Terms]) AND ((y_5[Filter]) AND (clinicalstudy[Filter] OR clinicaltrial[Filter] OR comparativestudy[Filter] OR consensusdevelopmentconference[Filter] OR controlledclinicaltrial[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR practiceguideline[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))	599
7/10/2022	PubMed	All	((("palivizumab/therapeutic use"[MeSH Terms] AND "heart defects, congenital"[MeSH Terms] AND "respiratory syncytial viruses"[MeSH Terms]) OR "heart defects, congenital/complications"[MeSH Terms] OR "palivizumab"[MeSH Terms]) AND ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "infant newborn"[All Fields])) AND ((y_5[Filter]) AND (clinicalstudy[Filter] OR clinicaltrial[Filter] OR comparativestudy[Filter] OR consensusdevelopmentconference[Filter] OR controlledclinicaltrial[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR practiceguideline[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))	125
7/10/2022	PubMed	All	("palivizumab"[MeSH Terms] AND "heart defects, congenital"[MeSH Terms]) AND ("respiratory syncytial viruses"[MeSH Terms]) AND "infant"[MeSH Terms]	21
7/10/2022	PubMed	All	(("heart defects, congenital"[MeSH Terms] OR ("heart"[All Fields] AND "defects"[All Fields] AND "congenital"[All Fields]) OR "congenital heart defects"[All Fields] OR ("congenital"[All Fields] AND "heart"[All Fields] AND "disease"[All Fields]) OR "congenital heart disease"[All Fields]) AND ("palivizumab"[MeSH Terms] OR "palivizumab"[All Fields]) AND ("respiratory syncytial viruses"[MeSH Terms] OR ("respiratory"[All Fields] AND "syncytial"[All Fields] AND "viruses"[All Fields]) OR "respiratory syncytial viruses"[All Fields] OR ("respiratory"[All Fields] AND "syncytial"[All Fields] AND "virus"[All Fields]) OR "respiratory syncytial virus"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infant s"[All Fields])) AND ((y_5[Filter]) AND (clinicalstudy[Filter] OR clinicaltrial[Filter] OR comparativestudy[Filter] OR consensusdevelopmentconference[Filter] OR controlledclinicaltrial[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR practiceguideline[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))	17

7/10/2022	PubMed	All	((("palivizumab administration"[All Fields] AND ("dosage"[All Fields] OR "dosages"[All Fields])) OR "palivizumab/therapeutic use"[MeSH Terms]) AND "respiratory syncytial virus infections/prevention and control"[MeSH Terms] AND ("controling"[All Fields] OR "controllability"[All Fields] OR "controllable"[All Fields] OR "controllably"[All Fields] OR "controller"[All Fields] OR "controllers"[All Fields] OR "controlling"[All Fields] OR "controls"[All Fields] OR "prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "control"[All Fields] OR "control groups"[MeSH Terms] OR ("control"[All Fields] AND "groups"[All Fields]) OR "control groups"[All Fields]) AND ("heart defects, congenital"[MeSH Terms] OR ("heart"[All Fields] AND "defects"[All Fields] AND "congenital"[All Fields]) OR "congenital heart defects"[All Fields] OR ("congenital"[All Fields] AND "heart"[All Fields] AND "disease"[All Fields]) OR "congenital heart disease"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infant s"[All Fields])) AND ((y_5[Filter]) AND (clinicalstudy[Filter] OR clinicaltrial[Filter] OR comparativestudy[Filter] OR consensusdevelopmentconference[Filter] OR controlledclinicaltrial[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR practiceguideline[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))	15
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7/10/2022	Embase	All	('palivizumab'/exp OR palivizumab) AND ('respiratory syncytial virus infections'/exp OR 'respiratory syncytial virus infections' OR (('respiratory'/exp OR respiratory) AND syncytial AND ('virus'/exp OR virus) AND ('infections'/exp OR infections))) AND ('congenital heart disease'/exp OR 'congenital heart disease' OR (('congenital'/exp OR congenital) AND ('heart'/exp OR heart) AND ('disease'/exp OR disease))) AND ('infant'/exp OR infant) AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [systematic review]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim) AND [2017-2022]/py	16
7/10/2022	Embase	All	palivizumab'/de AND 'congenital heart disease'/de AND 'infant'/de AND 'respiratory syncytial virus infection'/de	87
7/10/2022	Embase	All	#3 AND (2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py) AND ('cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'meta analysis'/de OR 'practice guideline'/de OR 'systematic review'/de)	29
7/10/2022	Web Of Science	All	congenital heart disease AND palivizumab AND respiratory syncytial virus	211
7/10/2022	Web of Science	All	congenital heart disease AND palivizumab AND respiratory syncytial virus -keyword plus	2
7/10/2022	Web of Science	All	palivizumab AND heart defects congenital AND infant	2
7/10/2022	ClinicalKey	CPG	congenital heart disease complications	9
8/10/2022	Ebscohost	All	Congenital heart disease AND infant AND palivizumab/limite 2018-2023/revistas	5
8/10/2022	PubMed	All	Palivizumab AND prophylaxis AND respiratory syncytial virus infection AND younger AND congenital heart disease	5
8/10/2022	Science Direct	All	Palivizumab AND prophylaxis AND respiratory syncytial virus infection AND younger AND congenital heart disease	48
8/10/2022	Cochrane	SLR	Congenital heart disease AND infant AND palivizumab	1
8/10/2022	Cochrane	SLR	Palivizumab in Title Abstract Keyword - with Cochrane Library publication date Between Jan 2017 and Oct 2022, in Cochrane Reviews, Trials (Word variations have been searched)	2
8/10/2022	Cochrane	SLR	MeSH descriptor: [Palivizumab] explode all trees and with qualifier(s): [administration & dosage - AD]	2
8/10/2022	PubMed	All	(("palivizumab/administration and dosage"[MeSH Terms] OR "palivizumab/therapeutic use"[MeSH Terms]) AND "respiratory syncytial virus infections/prevention and control"[MeSH Terms] AND "heart defects, congenital"[MeSH Terms]) AND (y_5[Filter])	9

8/10/2022	PubMed	All	(("palivizumab/administration and dosage"[MeSH Terms] OR "palivizumab/therapeutic use"[MeSH Terms]) AND "heart defects, congenital/complications"[MeSH Terms]) AND (y_5[Filter])	5
8/10/2022	Science Direct	All	palivizumab/administration and dosage OR palivizumab/therapeutic use AND respiratory syncytial virus infections/prevention and control AND heart defects, congenital AND ((y_5[Filter])	124
1/12/2022	Google Scholar	All	Infants with hemodynamically significant congenital heart disease AND risk of respiratory syncytial virus hospitalization	65
10/12/2022	PubMed	All	(("test s"[All Fields] OR "tested"[All Fields] OR "testing"[All Fields] OR "testings"[All Fields] OR "tests"[All Fields]) AND ("detect"[All Fields] OR "detectabilities"[All Fields] OR "detectability"[All Fields] OR "detectable"[All Fields] OR "detectables"[All Fields] OR "detectably"[All Fields] OR "detected"[All Fields] OR "detectible"[All Fields] OR "detecting"[All Fields] OR "detection"[All Fields] OR "detections"[All Fields] OR "detects"[All Fields]) AND ("heart defects, congenital"[MeSH Terms] OR ("heart"[All Fields] AND "defects"[All Fields] AND "congenital"[All Fields]) OR "congenital heart defects"[All Fields] OR ("congenital"[All Fields] AND "heart"[All Fields] AND "defects"[All Fields]))) AND (y_5[Filter])	533
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10/12/2022	PubMed	SLR	("heart defects, congenital/diagnosis"[MeSH Terms] AND ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "newborn"[All Fields] OR "newborns"[All Fields] OR "newborn s"[All Fields])) AND ((y_5[Filter]) AND (systematicreview[Filter]))	21
10/12/2022	PubMed	SLR	(("test s"[All Fields] OR "tested"[All Fields] OR "testing"[All Fields] OR "testings"[All Fields] OR "tests"[All Fields]) AND ("detect"[All Fields] OR "detectabilities"[All Fields] OR "detectability"[All Fields] OR "detectable"[All Fields] OR "detectables"[All Fields] OR "detectably"[All Fields] OR "detected"[All Fields] OR "detectible"[All Fields] OR "detecting"[All Fields] OR "detection"[All Fields] OR "detections"[All Fields] OR "detects"[All Fields]) AND ("heart defects, congenital"[MeSH Terms] OR ("heart"[All Fields] AND "defects"[All Fields] AND "congenital"[All Fields]) OR "congenital heart defects"[All Fields] OR ("congenital"[All Fields] AND "heart"[All Fields] AND "defects"[All Fields]))) AND (systematicreview[Filter])	27
10/12/2022	PubMed	All	(("detect"[All Fields] OR "detectabilities"[All Fields] OR "detectability"[All Fields] OR "detectable"[All Fields] OR "detectables"[All Fields] OR "detectably"[All Fields] OR "detected"[All Fields] OR "detectible"[All Fields] OR "detecting"[All Fields] OR "detection"[All Fields] OR "detections"[All Fields] OR "detects"[All Fields]) AND ("heart defects, congenital"[MeSH Terms] OR ("heart"[All Fields] AND "defects"[All Fields] AND "congenital"[All Fields]) OR "congenital heart defects"[All Fields] OR ("congenital"[All Fields] AND "heart"[All Fields] AND "disease"[All Fields]) OR "congenital heart disease"[All Fields]) AND (("cardiologi"[All Fields] OR "cardiologie"[All Fields] OR "cardiology"[MeSH Terms] OR "cardiology"[All Fields] OR "cardiology s"[All Fields]) AND ("diagnosis"[MeSH Subheading] OR "diagnosis"[All Fields] OR "screening"[All Fields] OR "mass screening"[MeSH Terms] OR ("mass"[All Fields] AND "screening"[All Fields]) OR "mass screening"[All Fields] OR "early detection of cancer"[MeSH Terms] OR ("early"[All Fields] AND "detection"[All Fields] AND "cancer"[All Fields]) OR "early detection of cancer"[All Fields] OR "screen"[All Fields] OR "screenings"[All Fields] OR "screened"[All Fields] OR "screens"[All Fields]))) AND (2020:2023[pdat])	496
3/01/2022	PubMed	All	(("palivizumab"[MeSH Terms] OR "palivizumab"[All Fields]) AND ("prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prophylaxis"[All Fields] OR "prophylaxies"[All Fields] OR "prophylaxy"[All Fields]) AND ("cardiomyopathie"[All Fields] OR "cardiomyopathies"[MeSH Terms] OR "cardiomyopathies"[All Fields] OR "cardiomyopathy"[All Fields])) AND ((humans[Filter]) AND (2018/1/1:2023/1/5[pdat]) AND (english[Filter] OR spanish[Filter]))	0

3/01/2022	PubMed	All	("palivizumab"[MeSH Terms] OR (("palivizumab"[MeSH Terms] OR "palivizumab"[All Fields]) AND ("prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prophylaxis"[All Fields] OR "prophylaxies"[All Fields] OR "prophylaxy"[All Fields]))) AND "heart defects, congenital"[MeSH Terms]	65
3/01/2022	PubMed	All	(("palivizumab"[MeSH Terms] OR "palivizumab"[All Fields]) AND ("prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prophylaxis"[All Fields] OR "prophylaxies"[All Fields] OR "prophylaxy"[All Fields])) AND ((humans[Filter]) AND (2018/1/1:2023/1/5[pdat]) AND (english[Filter] OR spanish[Filter]))	174
3/01/2022	PubMed	All	(("palivizumab"[MeSH Terms] OR "palivizumab"[All Fields]) AND ("prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prophylaxis"[All Fields] OR "prophylaxies"[All Fields] OR "prophylaxy"[All Fields]) AND ("heart defects, congenital"[MeSH Terms] OR ("heart"[All Fields] AND "defects"[All Fields] AND "congenital"[All Fields]) OR "congenital heart defects"[All Fields] OR ("heart"[All Fields] AND "defects"[All Fields] AND "congenital"[All Fields]) OR "heart defects congenital"[All Fields])) AND (english[Filter] OR spanish[Filter])	57
4/01/2022	Science Direct	All	congenital heart disease AND palivizumab prophylaxis AND respiratory syncytial virus AND infants. Year: 2018-2023, Article type: Review articles, Research articles	48
4/01/2022	Epistemonikos	All	palivizumab AND congenital heart disease) (title:(palivizumab AND heart defects, congenital OR palivizumab prophylaxis) OR abstract:(palivizumab AND heart defects, congenital OR palivizumab prophylaxis))	9
6/01/2022	PubMed	All	(("respiratory syncytial viruses"[MeSH Terms] OR ("respiratory"[All Fields] AND "syncytial"[All Fields] AND "viruses"[All Fields]) OR "respiratory syncytial viruses"[All Fields] OR ("respiratory"[All Fields] AND "syncytial"[All Fields] AND "virus"[All Fields]) OR "respiratory syncytial virus"[All Fields]) AND (("palivizumab"[MeSH Terms] OR "palivizumab"[All Fields]) AND ("prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prophylaxis"[All Fields] OR "prophylaxies"[All Fields] OR "prophylaxy"[All Fields])) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infant s"[All Fields])) AND ((y_5[Filter]) AND (clinicaltrial[Filter] OR comparativestudy[Filter] OR consensusdevelopmentconference[Filter] OR controlledclinicaltrial[Filter] OR guideline[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR practiceguideline[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]))	78
6/01/2022	PubMed	All	(("palivizumab"[MeSH Terms] OR "palivizumab"[All Fields]) AND ("prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prophylaxis"[All Fields] OR "prophylaxies"[All Fields] OR "prophylaxy"[All Fields])) AND ((y_5[Filter]) AND (clinicaltrial[Filter] OR comparativestudy[Filter] OR consensusdevelopmentconference[Filter] OR controlledclinicaltrial[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))	51
6/01/2022	PubMed	All	("transplantability"[All Fields] OR "transplantable"[All Fields] OR "transplantated"[All Fields] OR "transplantating"[All Fields] OR "transplantation"[MeSH Terms] OR "transplantation"[All Fields] OR "transplantations"[All Fields] OR "transplanted"[All Fields] OR "transplanting"[All Fields] OR "transplantation"[MeSH Subheading] OR "transplantation s"[All Fields] OR "transplanter"[All Fields] OR "transplanters"[All Fields] OR "transplantion"[All Fields] OR "transplants"[MeSH Terms] OR "transplants"[All Fields] OR "transplant"[All Fields]) AND ("palivizumab"[MeSH Terms] OR "palivizumab"[All Fields]) AND ("heart defects, congenital"[MeSH Terms] OR ("heart"[All Fields] AND "defects"[All Fields] AND "congenital"[All Fields]) OR "congenital heart defects"[All Fields] OR ("congenital"[All Fields] AND "heart"[All Fields] AND "disease"[All Fields]) OR "congenital heart disease"[All Fields])	6
6/01/2022	PubMed	All	("transplantability"[All Fields] OR "transplantable"[All Fields] OR "transplantated"[All Fields] OR "transplantating"[All Fields] OR "transplantation"[MeSH Terms] OR "transplantation"[All Fields] OR "transplantations"[All Fields] OR "transplanted"[All Fields] OR "transplanting"[All Fields] OR "transplantation"[MeSH Subheading] OR "transplantation s"[All Fields] OR "transplanter"[All Fields] OR "transplanters"[All Fields] OR "transplantion"[All Fields] OR "transplants"[MeSH Terms] OR "transplants"[All Fields] OR "transplant"[All Fields]) AND ("heart"[MeSH Terms] OR "heart"[All Fields] OR "hearts"[All Fields] OR "heart s"[All Fields]) AND ("palivizumab"[MeSH Terms] OR "palivizumab"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infant s"[All Fields])	9

21/01/2022	PubMed	All	('respiratory syncytial virus prophylaxis' OR (('respiratory'/exp OR respiratory) AND syncytial AND ('virus'/exp OR virus) AND ('prophylaxis'/exp OR prophylaxis))) AND congenital heart disease	219
21/01/2022	PubMed	All	(("significance"[All Fields] OR "significances"[All Fields] OR "significant"[All Fields] OR "significants"[All Fields]) AND ("heart defects, congenital"[MeSH Terms] OR ("heart"[All Fields] AND "defects"[All Fields] AND "congenital"[All Fields]) OR "congenital heart defects"[All Fields] OR ("congenital"[All Fields] AND "heart"[All Fields] AND "disease"[All Fields]) OR "congenital heart disease"[All Fields]) AND ("palivizumab"[MeSH Terms] OR "palivizumab"[All Fields])) AND (y_5[Filter])	28
21/01/2022	PubMed	All	(("palivizumab"[MeSH Terms] OR "palivizumab"[All Fields]) AND ("heart defects, congenital"[MeSH Terms] OR ("heart"[All Fields] AND "defects"[All Fields] AND "congenital"[All Fields]) OR "congenital heart defects"[All Fields] OR ("congenital"[All Fields] AND "heart"[All Fields] AND "disease"[All Fields]) OR "congenital heart disease"[All Fields])) AND (y_5[Filter])	51
21/02/2022	Ebscohost	All	(('palivizumab'/exp OR palivizumab) AND ('prophylaxis'/exp OR prophylaxis) AND reduces AND ('hospitalization'/exp OR hospitalization) AND due AND to AND ('respiratory'/exp OR respiratory) AND syncytial AND ('virus'/exp OR virus) AND in AND young AND ('children'/exp OR children) AND with AND hemodynamically AND significant AND ('congenital'/exp OR congenital) AND ('heart'/exp OR heart) AND ('disease'/exp OR disease))	152

Annex 3. Expert opinion voting results

Opinion		Scale	Recommendation 1	Recommendation 2	Recommendation 3
Domain 1	Do the desirable effects of the recommendations outweigh the undesirable effects?	No			
		Probably not			
		Not sure			
		Probably yes		6.7	
		Yes	100	93.3	100
		It depends			
		Conclusion	Strong	Strong	Strong
Domain 2	Could fewer resources be needed to implement the recommendations than to treat the health effects of not implementing them within healthcare provision?	No			
		Probably not			
		Not sure			
		Probably yes		6.7	6.7
		Yes	100	93.3	93.3
		It depends			
		Conclusion	Strong	Strong	Strong
Domain 3	Are the recommendations acceptable to include in clinical practice for all the interested parties (patients, healthcare professionals and decision makers)?	No			
		Probably not			
		Not sure			
		Probably yes		6.7	6.7
		Yes	100	93.3	93.3
		It depends			
		Conclusion	Strong	Strong	Strong

Domain 4	Could the recommendations be implemented in all risk groups with few restrictions in the healthcare system?	No			
		Probably not		6.7	
		Not sure			
		Probably yes	53.3	46.7	40.0
		Yes	46.7	40.0	53.3
		It depends		6.7	6.7
		Conclusion	Weak	Weak	Weak
	Average vote and resulting conclusion	Total score Yes	346.70	319.90	339.90
		No	0	0	0
		Probably not	0	1.68	0
		Not sure	0	0	0
		Probablyyes	13.33	16.70	13.35
		Yes	86.68	79.95	84.98
		It depends	0	1.68	1.68
		Conclusion	Weak	Weak	Weak

Opinion		Scale	Recommendation 4	Recommendation 5	Recommendation 6
Domain 1	Do the desirable effects of the recommendations outweigh the undesirable effects?	No			
		Probably not			
		Not sure			
		Probably yes		6.7	6.7
		Yes	100	93.3	93.3
		It depends			
		Conclusion	Strong	Strong	Strong
Domain 2	Could fewer resources be needed to implement the recommendations than to treat the health effects of not implementing them within healthcare provision?	No			
		Probably not			
		Not sure			
		Probably yes	6.7	6.7	6.7
		Yes	93.3	93.3	93.3
		It depends			
		Conclusion	Strong	Strong	Strong
Domain 3	Are the recommendations acceptable to include in clinical practice for all the interested parties (patients, healthcare professionals and decision makers)?	No			
		Probably not			
		Not sure			
		Probably yes	6.7	13.3	13.3
		Yes	93.3	86.7	86.7
		It depends			
		Conclusion	Strong	Weak	Weak
Domain 4	Could the recommendations be implemented in all risk groups with few restrictions in the healthcare system?	No			
		Probably not			
		Not sure			
		Probably yes	33.3	21.4	33.3
		Yes	66.7	71.4	66.7
		It depends		7.1	
		Conclusion	Weak	Weak	Weak

	Average vote and resulting conclusion	Total score Yes	353.30	344.70	340.00
		No	0	0	0
		Probably not	0	0	0
		Not sure	0	0	0
		Probably yes	11.68	12.05	15.00
		Yes	88.33	86.18	85.00
		It depends	0	1.78	0
		Conclusion	Weak	Weak	Weak

Opinion		Scale	Recommendation 7	Recommendation 8	Recommendation 9
Domain 1	Do the desirable effects of the recommendations outweigh the undesirable effects?	No			
		Probably not			
		Not sure			
		Probably yes	6.7	6.7	6.7
		Yes	93.3	93.3	93.3
		It depends			
		Conclusion	Strong	Strong	Strong
Domain 2	Could fewer resources be needed to implement the recommendations than to treat the health effects of not implementing them within healthcare provision?	No			
		Probably not			
		Not sure			
		Probably yes	20.0	13.3	6.7
		Yes	80.0	86.7	93.3
		It depends			
		Conclusion	Weak	Weak	Strong
Domain 3	Are the recommendations acceptable to include in clinical practice for all the interested parties (patients, healthcare professionals and decision makers)?	No			
		Probably not			
		Not sure			
		Probably yes	13.3	26.7	6.7
		Yes	86.7	73.3	93.3
		It depends			
		Conclusion	Weak	Weak	Strong
Domain 4	Could the recommendations be implemented in all risk groups with few restrictions in the healthcare system?	No			
		Probably not			
		Not sure		6.7	
		Probably yes	33.3	20.0	33.3
		Yes	60.0	66.7	60.0
		It depends	6.7	6.7	6.7
		Conclusion	Weak	Weak	Weak
	Average vote and resulting conclusion	Total score Yes	320.00	320.00	339.90
		No	0	0	0
		Probably not	0	0	0
		Not sure	0	1.65	0
		Probably yes	18.33	16.68	13.35
		Yes	80.00	80.00	84.98
		It depends	1.68	1.68	1.68
		Conclusion	Weak	Weak	Weak

	Opinion	Scale	Recommendation 10	Recommendation 11	Recommendation 12	Recommendation 13
Domain 1	Do the desirable effects of the recommendations outweigh the undesirable effects?	No				
		Probably not				
		Not sure				
		Probably yes			20.0	
		Yes	100	100	80.0	100
		It depends				
		Conclusion	Strong	Strong	Weak	Strong
Domain 2	Could fewer resources be needed to implement the recommendations than to treat the health effects of not implementing them within healthcare provision?	No				
		Probably not	6.7			
		Not sure				
		Probably yes	13.3	6.7	20.0	6.7
		Yes	80.00	93.3	80.0	93.3
		It depends				
		Conclusion	Weak	Strong	Weak	Strong
Domain 3	Are the recommendations acceptable to include in clinical practice for all the interested parties (patients, healthcare professionals and decision makers)?	No				
		Probably not				
		Not sure				
		Probably yes	20.0	13.3	20.0	6.7
		Yes	80.0	86.7	80.0	93.3
		It depends				
		Conclusion	Weak	Weak	Weak	Strong
Domain 4	Could the recommendations be implemented in all risk groups with few restrictions in the healthcare system?	No				
		Probably not	6.7			
		Not sure				
		Probably yes	13.3	26.7	26.7	26.7
		Yes	73.3	66.7	73.3	66.7
		It depends	6.7	6.7		6.7
		Conclusion	Weak	Weak	Weak	Weak
	Average vote and resulting conclusion	Total Score Yes	333.30	346.70	313.30	353.30
		No	0	0	0	0
		Probably not	3.35	0	0	0
		Not sure	0	0	0	0
		Probably yes	11.65	11.66	21.66	10.00
		Yes	83.33	86.66	78.35	88.33
		It depends	1.68	1.68	0	1.68
		Conclusion	Weak	Weak	Weak	Weak

Conflict of Interest Statement

This formal, evidence-based and expert consensus on immunoprophylaxis with palivizumab in patients with congenital heart disease received funding from AstraZeneca Colombia, which provided funds to Sociedad Colombiana de Cardiología y Cirugía Cardiovascular for academic advances in the field of pediatric cardiology. AstraZeneca Colombia has not participated in any of the design phases, decision making, development of materials, bibliography analysis, panel member selection, panel activity nor drafting of the report and document.

A total of 15 experts in pediatric cardiology from different parts of Colombia took part in the consensus, with the aim of embracing experiences from the entire Colombian territory. Thus, a group of professionals was consolidated with the most experience in the use of the medication in question, as well as academic

and professional credentials, in cities like Medellín, Bogotá, Popayán, Cali, Cartagena, Pasto, Barranquilla, Cúcuta, Floridablanca and Montería. It should be noted that the participating experts did not receive any financial compensation for conducting this activity from the industry, nor are they industry employees.

In addition, Odds Epidemiology, SAS provided methodological support throughout the implementation and development of the consensus since it began on September 24, 2022, when the consensus launching meeting was held on site along with the presentation and definition of the participants' roles and the definition of the research questions and their scope. Subsequently, a total of seven virtual panels were held, with an average of 92% of the experts participating in each. These meetings lasted an average of two hours, during which the group of methodologists explained the evidence synthesis performed, for subsequent formal discussion amongst the experts in panels, in order to produce evidence-based recommendations evaluated by expert opinion.

The participants signed data confidentiality, data protection and conflict of interest documents in October 2022. This task was done by all participants and the group of methodologists. Each participant carried out this process digitally.

Finally, it is important to state that the project sponsor paid its total contribution to Sociedad Colombiana de Cardiología, where the resources were only directed to the Odds Epidemiology group, who performed all the support, development and implementation tasks of the activities established in the methodology. The participating experts received no financial compensation during the implementation of this project.

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