

Peer Review File

Article information: <https://dx.doi.org/10.21037/asj-21-70>

Reviewer A

The narrative review presents the socioeconomical, financial and organizational aspects of highly specialized services such as congenital cardiac surgery (CHS). In this discipline close relationship between quality (=patient outcomes) and quantity (=surgical output of a center) is well known and has been reconfirmed in numerous previous studies. The manuscript is well-written, adheres to the requirements of a narrative review.

1. The paper seems to aim to provide a global perspective on regionalization of CHS, however, the reader receives a clear view about the situation in the US and a much-blurred picture about the 'rest of the world'. Nevertheless, as CHS services are in the state of establishment in many countries, it would be an opportunity to present the infrastructural, financing, etc. framework these processes can successfully happen. There are numerous examples worldwide that authors may reference. The paper mainly focuses on the regionalization the tertiary-care centers (where CHS is actually performed) and other levels of care e.g., diagnostic and after-care aspects are not discussed. I believe the entire continuum-of-care is important, e.g., late-referrals, inadequate interstage surveillance being strong pushers of adverse outcomes.

Response:

Thank you for your comment. Regarding the comment about the 'blurriness' of the rest of the world, we agree that there are still many questions about how care is delivered. We have tried to provide references for those areas in which this investigative team has direct experience or knowledge. We have amended our methodology, added a segment on the international state of congenital heart surgery, challenges facing regionalization and a segment on potential avenues for future research.

Changes to the Manuscript:

1. Methods: Page 5, Lines 96-110
"PubMed was used to search articles pertaining to congenital cardiac surgery, regionalization, financing infant heart surgery, ethical challenges, as well as international implications published in the last 20 years. To ensure a comprehensive review, our search strategy combined 'congenital heart surgery' AND 'regionalization' OR 'centralization' AND 'healthcare policy'. Inclusion criteria included a manuscript (commentary, editorial, systematic review, meta-analysis, original article, review, book chapter, government publication, legislative documents) published in English between 1/1/2001 and 08/31/2021. Exclusion criteria included articles published outside the time period listed, or publications within the time period that focused on other pediatric surgical sub-specialties, regionalization in stroke and other surgical sub-specialties and healthcare policy unrelated to congenital heart disease.

Our NCBI, PubMed search yielded 944 studies. Of these, 38 articles met the inclusion criteria and were thus used in our paper."

2. International State of Congenital Heart Surgery (Page 12, Lines 298-344)

“The international arena of CHS regionalization is yet to be established. Given the significant gaps surrounding the availability of services and the varying factors influencing CHD outcomes in low-resource settings, it is helpful to assess the international landscape with a 30,000 foot view. Factors such as lack of cardiac surgery centers in several low- and middle- income countries, high cost of care and concomitant lack of insurance schemes capable of covering CHD repair services, lead to important hardships for families and patients [18]. These factors contribute to late case presentations; patients additionally present with comorbid conditions, making them particularly challenging to local teams not equipped with the knowledge and techniques to address them. Combined with limited resources and understaffing in existing centers [18], ensuring optimal outcomes in such low-resource settings is severely challenged.

In one study on CHD neonatal outcomes in Western India between 2009 and 2011, one significant predictor of mortality was incomplete repair of CHD lesions [19]. Other challenges discussed by the authors were late presentation of patients, with only 5% diagnosed in the antenatal stage [19]. Interestingly, mode of transportation, i.e. private versus transport ambulance did not impact mortality [19]. Furthermore, the total burden of CHS in India remains speculative, given the lack of national registries and an urgent need for them [20].

Other challenges facing CHS in low-resource settings include prolonged waiting time until surgery and paucity of human resources. In Thailand, median waiting time for pediatric patients referred for cardiac surgery was 195 days, with a 5% mortality at 2 years while waiting [21]. Such phenomena are a threat to public health and attempts to resolve such challenges should ideally be made at the national level, in collaboration with international societies and experts. The paucity of human resources was highlighted in a survey of cardiac surgeons and residents in Nigeria, which showed the daunting need for pediatric cardiac surgery centers in the setting of a weak national health system, and poor human resources. Respondents emphasized the need for local and international partnerships with country leadership in hopes of advancing care for the pediatric population [22]. Such barriers emphasize the urgent need to focus attention on low-resource settings, to ensure timely and high quality access to CHS services.

Both the wealth of a nation and the size of its population contribute to the ability to provide specialized care. Five out of 58 small, developing island states, have only local health centers, which are dependent on and served by visiting surgeons. Aruba has no local cardiac surgery center, necessitating the state to send its cardiac patients abroad, costing it 12% of its total healthcare expenditure [23]. While itinerate surgeons provide a needed service, the model is unable to fill the needs of these nations.

Access to treatment for CHD in sub-Saharan Africa within two years of birth is <1% [24]. Nearly 300,486 infants are born annually in Africa with CHD [25]. Even though surgical palliation of

functionally single ventricle patients can improve survival, children with these severe lesions have very poor care coverage in the African region because such care is expensive and therefore is not highly prioritized by policymakers from a cost-effectiveness perspective [26, 27]. Thus, ongoing education, collaboration with international societies, local civil society and policy makers is vital if progress in access to CHD surgical services is to be increased.

The global challenges discussed above demonstrate an urgent need for international collaboration between local CHD physicians, economic and ethnical experts to establish and/or advance access to CHS services within many burgeoning healthcare systems. The proposed structures, which should include centralization, will be variable and should be tailored to the needs of every country based on its national health system, population demographics, infrastructure, and insurance schemes used.”

3. International Implications of Regionalization (Page 13, Lines 379-388)

“An additional example of regionalization in a high-income country includes the Japan experience, which has demonstrated promise in the arena of regionalization. In its 2015-2016 status of cardiac surgery, the Japanese cardiovascular surgery database demonstrated that complex procedures, such as the Norwood, Rastelli and bidirectional Glenn were solely taking place at high volume centers. Despite this fact, complication rates, such as unplanned cardiac reoperation and phrenic nerve paralysis were still considerable, requiring further efforts for improvement [30]. Such data highlights that regionalization efforts hold promise, but require continuous monitoring to ensure the provision of the highest CHS quality possible for patients.”

4. Key Areas of Focus for Future Research (Page 14-15, Lines 427, 459)

“A clearer understanding of methods to curtail challenges faced by patients in low- and middle-income countries is needed. The full spectrum of CHS requires attention on several levels: timeliness of diagnosis, availability of modes of transportation, respective infrastructure, availability of resources, technical expertise, and the structure of postoperative surveillance. Situational analyses focused on these topics would be important in either the development of national healthcare delivery programs, or the modification of existing paradigms. Furthermore, data regarding the aforementioned areas and desired states should be coupled with a plan aimed at reforming overall health policy and governance structure within each country and region, as well as mechanisms to ensure accountability.

Coupling of these interests have been successfully used previously. It has been shown that further collaboration with political institutions is needed to advance the use of health evidence in policymaking [37]. In 2016, the World Society for Pediatric and Congenital Heart Surgery established its plan for international exchange of trainees to enhance international surgical education and treatment missions in addition to a potential system for global certification of its surgeons to facilitate movement of skill to areas of need [38]. Such plans are promising and future research efforts can potentially collaborate with global surgical technical experts to ensure that

international efforts, such as the one announced by the World Society, are supported with the relevant expertise to set up local, national and regional capacity building mechanisms. Research could also focus on assessing the impact of such interventions and disseminating lessons learned to nearby regions or nearby countries in the same region. For example, the ‘Partnership for the Heart’ training initiative between Germany and Estonia demonstrated a 28% reduction in infant mortality secondary to congenital heart disease at 50% the cost incurred if the patients had to leave Estonia to seek care [39].

Multiple other areas of research also will be critical to understanding the impact of regionalization. Studying whether socioeconomic status and race are impacted adversely by regionalization, a potentially large challenge, are needed. Investigating the potential presence of an inflection point at which surgical volumes exceed the ability of a center to ensure top quality care, especially in low resource settings, where centers may have an excessive number of cases, will be important. The high volume of cases done in some LMIC will potentially facilitate the discovery of such an inflection point – although this will depend on the surrounding infrastructure to be evolved to a point where these systems can be compared to those of a developed country.”

2. I have few specific comments: Lines 136-143: the financial remuneration of surgeons is an interesting aspect, but it is hardly relevant to the scope of regionalization CHS. Congenital cardiac surgeons may be the pushers for regionalization in anticipating a higher pay, however, I believe this aspect is on the wrong side of the argumentation, i.e., centralization should be directed to an improved care rather than an improved salary. I propose to rephrase or remove this section.

Response:

Thank you for your comment. We have added a segment and linked a new study as well towards the end of this section.

Changes to the Manuscript:

1. Congenital Cardiac Surgery Financing (Page 6, Lines 148-153):
“Nevertheless, despite effective centralization being important, it should not be solely market driven, but focused on providing multi-disciplinary treatment of complex disease with around the clock availability of trained specialists.”

Additional reference: Vonlanthen R, Lodge P, Barkun JS, Farges O, Rogiers X, Soreide K, Kehlet H, Reynolds JV, Käser SA, Naredi P, Borel-Rinkes I, Biondo S, Pinto-Marques H, Gnant M, Nafteux P, Ryska M, Bechstein WO, Martel G, Dimick JB, Krawczyk M, Oláh A, Pinna AD, Popescu I, Puolakkainen PA, Sotiropoulos GC, Tukiainen EJ, Petrowsky H, Clavien PA. Toward a Consensus on Centralization in Surgery. *Ann Surg.* 2018 Nov;268(5):712-724. doi: 10.1097/SLA.0000000000002965. PMID: 30169394.

3. Lines 193-196: parabolic association between household income and patient outcome is –

again – a very interesting observation. I, however, find the supportive argument – i.e., well-to-do parents are able to travel to centers with high reputation – extremely weak. I wonder whether authors looked into other aspects, e.g., parental age (both parents), overall higher complexity, associated anomalies, etc.

Response:

Thank you for your comment. The data from our prior study simply shows that this is objectively the case – the potential reasons for this, as the reviewer points out, are speculative and were offered as one explanation that requires further study. Regarding the other comments, we did not look at parental age as that is not available in the PHIS data, but we did look at associated genetic defects and anomalies. We have clarified that this is a potential underlying reason for the parabolic relationship of income to outcome. (lines 209-210).

4. Lines 280-284: I propose that the term ‘budget’ is a rather broad and unspecific term. Most of the low-middle-income-countries suffer from underdeveloped infrastructure (general and healthcare), lack of an insurance system and, typically, government budget is not primarily utilized to cover healthcare expenditure, especially not for CHS.

Response:

Thank you for your comment. We have removed the word budget and replaced it with “resources allocated for healthcare”.

Changes to the Manuscript:

1. International Implications of Regionalization (Page 13, Lines 378-379).
“These countries have limited resources allocated for healthcare and therefore must distribute physical and human resources extremely efficiently.”

Reviewer B

This review aims to look at the current state of pediatric cardiac surgery in the U.S. and discusses the potential benefits and challenges by centralizing the surgical services.

I have the following comments:

1. The methods states that PubMed was used to look up articles pertaining to the topic. But the exact number of articles is not listed. Exact inclusion and exclusion criteria were not provided. Further details on the methods are suggested, even if this is a narrative review.

Response:

Thank you for your comment. We have amended our methodology accordingly.

Changes to the Manuscript:

1. Methods: Page 5, Lines 96-110

“PubMed was used to search articles pertaining to congenital cardiac surgery, regionalization, financing infant heart surgery, ethical challenges, as well as international implications published in the last 20 years. To ensure a comprehensive review, our search strategy combined ‘congenital heart surgery’ AND ‘regionalization’ OR ‘centralization’ AND ‘healthcare policy’. Inclusion criteria included a manuscript (commentary, editorial, systematic review, meta-analysis, original article, review, book chapter, government publication, legislative documents) published in English between 1/1/2001 and 08/31/2021. Exclusion criteria included articles published outside the time period listed, or publications within the time period that focused on other pediatric surgical sub-specialties, regionalization in stroke and other surgical sub-specialties and healthcare policy unrelated to congenital heart disease.

Our NCBI, PubMed search yielded 944 studies. Of these, 38 articles met the inclusion criteria and were thus used in our paper.”

2. The papers included was “papers done by publications by experts in the field”. I wonder if this thereby provide a highly selected material. Maybe the discussion would have benefitted by included of broader references (if they exists)?

Response:

Thank you for your comment. We concur that the use of selected papers is one source of bias. We have added a much more encompassing discussion on the international state of congenital heart surgery, challenges facing regionalization and a segment on potential avenues for future research. We have included several other references to support the comments in this embellished discussion.

Changes to the Manuscript:

Additional References Used:

- Vonlanthen R, Lodge P, Barkun JS, Farges O, Rogiers X, Soreide K, Kehlet H, Reynolds JV, Käser SA, Naredi P, Borel-Rinkes I, Biondo S, Pinto-Marques H, Gnani M, Naftoux P, Ryska M, Bechstein WO, Martel G, Dimick JB, Krawczyk M, Oláh A, Pinna AD, Popescu I, Puolakkainen PA, Sotiropoulos GC, Tukiainen EJ, Petrowsky H, Clavien PA. Toward a Consensus on Centralization in Surgery. *Ann Surg.* 2018 Nov;268(5):712-724. doi: 10.1097/SLA.0000000000002965. PMID: 30169394.
- Woo JL, Anderson BR, Gruenstein D, Conti R, Chua KP. Minimum Travel Distance Among Publicly Insured Infants with Severe Congenital Heart Disease: Potential Impact of In-state Restrictions. *Pediatr Cardiol.* 2019 Dec;40(8):1599-1608. doi: 10.1007/s00246-019-02193-1. Epub 2019 Aug 28. PMID: 31463514; PMCID: PMC6851488.
- Saxena A. Congenital cardiac surgery in the less privileged regions of the world. *Expert Rev Cardiovasc Ther.* 2009 Dec;7(12):1621-9. doi: 10.1586/erc.09.141. PMID: 19954323.
- Shukla VV, Bobhate P, Mohanty S, Rao S, Joshi P, Joshi V. Early Outcomes of Neonatal Cardiac Surgery in India. *Indian Pediatr.* 2020 Feb 15;57(2):129-132. PMID: 32060239.

- Raj S, Swaminathan S. Early Outcomes after Cardiac Surgery in Neonates and Infants in India. *Indian Pediatr.* 2020 Feb 15;57(2):117-118. PMID: 32060236.
- Khongphatthanayothin A, Layangool T, Sittiwangkul R, Pongprot Y, Lertsapcharoen P, Mokarapong P. Pediatric heart surgery waiting time in Thailand and its effect on mortality: A cooperative study from Chulalongkorn, Children and Chiang Mai University hospitals. *J Med Assoc Thai.* 2005 Sep;88 Suppl 4:S23-9. PMID: 16622997.
- Okonta KE, Tobin-West CI. Challenges with the establishment of congenital cardiac surgery centers in Nigeria: survey of cardiothoracic surgeons and residents. *J Surg Res.* 2016 May 1;202(1):177-81. doi: 10.1016/j.jss.2015.12.040. Epub 2015 Dec 30. PMID: 27083964.
- Vervoort D, Vinck EE, Tiwari KK, Tapaua N. Cardiac Surgery and Small Island States: A Bridge Too Far? *Ann Thorac Surg.* 2021 Mar;111(3):931-936. doi: 10.1016/j.athoracsur.2020.05.150. Epub 2020 Jul 25. PMID: 32721454.
- Edwin F, Entsua-Mensah K, Sereboe LA, Tettey MM, Aniteye EA, Tamatey MM, Adzamli I, Akyaa-Yao N, Gyan KB, Ofosu-Appiah E, Kotei D. Conotruncal Heart Defect Repair in Sub-Saharan Africa: Remarkable Outcomes Despite Poor Access to Treatment. *World J Pediatr Congenit Heart Surg.* 2016 Sep;7(5):592-9. doi: 10.1177/2150135116648309. PMID: 27587494.
- Edwin, F, Zühlke, L, Farouk, H. Status and challenges of care in Africa for adults with congenital heart defects. *World J Pediatr Congenit Heart Surg.* 2017;8(4):495–501.
- Edwin F, Elgamal MA, Dorra A, Reddy D, Entsua-Mensah K, Adzamli I, Yao NA, Tettey M, Tamatey M, Vosloo S, Kinsley R. Challenges of Caring for Functionally Single Ventricle Patients in Africa. *World J Pediatr Congenit Heart Surg.* 2019 May;10(3):338-342. doi: 10.1177/2150135118817769. PMID: 31084309.
- Edwin F. Palliation of Functionally Single Ventricle Patients in Sub-Saharan Africa-Is It Justifiable? *World J Pediatr Congenit Heart Surg.* 2019 Mar;10(2):171-173. doi: 10.1177/2150135119830006. PMID: 30841827.
- Hirata Y, Hirahara N, Murakami A, Motomura N, Miyata H, Takamoto S. Current status of cardiovascular surgery in Japan, 2015 and 2016: a report based on the Japan Cardiovascular Surgery Database. 1-congenital heart surgery. *Gen Thorac Cardiovasc Surg.* 2019 Sep;67(9):731-735. doi: 10.1007/s11748-019-01160-0. Epub 2019 Jul 20. PMID: 31327137.
- Iverson KR, Svensson E, Sonderman K, Barthélemy EJ, Citron I, Vaughan KA, Powell BL, Meara JG, Shrimpe MG. Decentralization and Regionalization of Surgical Care: A Review of Evidence for the Optimal Distribution of Surgical Services in Low- and Middle-Income Countries. *Int J Health Policy Manag.* 2019 Sep 1;8(9):521-537. doi: 10.15171/ijhpm.2019.43. PMID: 31657175; PMCID: PMC6815989.
- Liverani M, Hawkins B, Parkhurst JO. Political and institutional influences on the use of evidence in public health policy. A systematic review. *PLoS One.* 2013 Oct

30;8(10):e77404. doi: 10.1371/journal.pone.0077404. PMID: 24204823; PMCID: PMC3813708.

- Jonas RA. Strengthening International Collaboration in Congenital Heart Surgery. *World J Pediatr Congenit Heart Surg*. 2018 Jul;9(4):383-391. doi: 10.1177/2150135117696491. PMID: 29945516.
- Köhler F, Schierbaum C, Konertz W, Schneider M, Kern H, Int E, Tael K, Siigur U, Kleinfeld K, Bühlmeier K, Fotuhi P, Winter SF. Partnership for the heart. German-Estonian health project for the treatment of congenital heart defects in Estonia. *Health Policy*. 2005 Aug;73(2):151-9. doi: 10.1016/j.healthpol.2004.11.009. Epub 2004 Dec 16. PMID: 15978958.

Changes to the Manuscript:

1. International State of Congenital Heart Surgery (Page 12, Lines 298-344)

“The international arena of CHS regionalization is yet to be established. Given the significant gaps surrounding the availability of services and the varying factors influencing CHD outcomes in low-resource settings, it is helpful to assess the international landscape with a 30,000 foot view. Factors such as lack of cardiac surgery centers in several low- and middle- income countries, high cost of care and concomitant lack of insurance schemes capable of covering CHD repair services, lead to important hardships for families and patients [18]. These factors contribute to late case presentations; patients additionally present with comorbid conditions, making them particularly challenging to local teams not equipped with the knowledge and techniques to address them. Combined with limited resources and understaffing in existing centers [18], ensuring optimal outcomes in such low-resource settings is severely challenged.

In one study on CHD neonatal outcomes in Western India between 2009 and 2011, one significant predictor of mortality was incomplete repair of CHD lesions [19]. Other challenges discussed by the authors were late presentation of patients, with only 5% diagnosed in the antenatal stage [19]. Interestingly, mode of transportation, i.e. private versus transport ambulance did not impact mortality [19]. Furthermore, the total burden of CHS in India remains speculative, given the lack of national registries and an urgent need for them [20].

Other challenges facing CHS in low-resource settings include prolonged waiting time until surgery and paucity of human resources. In Thailand, median waiting time for pediatric patients referred for cardiac surgery was 195 days, with a 5% mortality at 2 years while waiting [21]. Such phenomena are a threat to public health and attempts to resolve such challenges should ideally be made at the national level, in collaboration with international societies and experts. The paucity of human resources was highlighted in a survey of cardiac surgeons and residents in Nigeria, which showed the daunting need for pediatric cardiac surgery centers in the setting of a weak national health system, and poor human resources. Respondents emphasized the need for local and international partnerships with country leadership in hopes of advancing care for the pediatric

population [22]. Such barriers emphasize the urgent need to focus attention on low-resource settings, to ensure timely and high quality access to CHS services.

Both the wealth of a nation and the size of its population contribute to the ability to provide specialized care. Five out of 58 small, developing island states, have only local health centers, which are dependent on and served by visiting surgeons. Aruba has no local cardiac surgery center, necessitating the state to send its cardiac patients abroad, costing it 12% of its total healthcare expenditure [23]. While itinerate surgeons provide a needed service, the model is unable to fill the needs of these nations.

Access to treatment for CHD in sub-Saharan Africa within two years of birth is <1% [24]. Nearly 300,486 infants are born annually in Africa with CHD [25]. Even though surgical palliation of functionally single ventricle patients can improve survival, children with these severe lesions have very poor care coverage in the African region because such care is expensive and therefore is not highly prioritized by policymakers from a cost-effectiveness perspective [26, 27]. Thus, ongoing education, collaboration with international societies, local civil society and policy makers is vital if progress in access to CHD surgical services is to be increased.

The global challenges discussed above demonstrate an urgent need for international collaboration between local CHD physicians, economic and ethnical experts to establish and/or advance access to CHS services within many burgeoning healthcare systems. The proposed structures, which should include centralization, will be variable and should be tailored to the needs of every country based on its national health system, population demographics, infrastructure, and insurance schemes used.”

2. International Implications of Regionalization (Page 13, Lines 379-388)

“An additional example of regionalization in a high-income country includes the Japan experience, which has demonstrated promise in the arena of regionalization. In its 2015-2016 status of cardiac surgery, the Japanese cardiovascular surgery database demonstrated that complex procedures, such as the Norwood, Rastelli and bidirectional Glenn were solely taking place at high volume centers. Despite this fact, complication rates, such as unplanned cardiac reoperation and phrenic nerve paralysis were still considerable, requiring further efforts for improvement [30]. Such data highlights that regionalization efforts hold promise, but require continuous monitoring to ensure the provision of the highest CHS quality possible for patients.”

3. Key Areas of Focus for Future Research (Page 14-15, Lines 427, 459)

“A clearer understanding of methods to curtail challenges faced by patients in low- and middle-income countries is needed. The full spectrum of CHS requires attention on several levels: timeliness of diagnosis, availability of modes of transportation, respective infrastructure, availability of resources, technical expertise, and the structure of postoperative surveillance. Situational analyses focused on these topics would be important in either the development of national healthcare delivery programs, or the modification of existing paradigms. Furthermore,

data regarding the aforementioned areas and desired states should be coupled with a plan aimed at reforming overall health policy and governance structure within each country and region, as well as mechanisms to ensure accountability.

Coupling of these interests have been successfully used previously. It has been shown that further collaboration with political institutions is needed to advance the use of health evidence in policymaking [37]. In 2016, the World Society for Pediatric and Congenital Heart Surgery established its plan for international exchange of trainees to enhance international surgical education and treatment missions in addition to a potential system for global certification of its surgeons to facilitate movement of skill to areas of need [38]. Such plans are promising and future research efforts can potentially collaborate with global surgical technical experts to ensure that international efforts, such as the one announced by the World Society, are supported with the relevant expertise to set up local, national and regional capacity building mechanisms. Research could also focus on assessing the impact of such interventions and disseminating lessons learned to nearby regions or nearby countries in the same region. For example, the ‘Partnership for the Heart’ training initiative between Germany and Estonia demonstrated a 28% reduction in infant mortality secondary to congenital heart disease at 50% the cost incurred if the patients had to leave Estonia to seek care [39].

Multiple other areas of research also will be critical to understanding the impact of regionalization. Studying whether socioeconomic status and race are impacted adversely by regionalization, a potentially large challenge, are needed. Investigating the potential presence of an inflection point at which surgical volumes exceed the ability of a center to ensure top quality care, especially in low resource settings, where centers may have an excessive number of cases, will be important. The high volume of cases done in some LMIC will potentially facilitate the discovery of such an inflection point – although this will depend on the surrounding infrastructure to be evolved to a point where these systems can be compared to those of a developed country.”

3. The authors summarize how race and social economic status have been linked to poor outcome after surgery. Further discussion on the potential impact on regionalization is suggested based on the actual numbers from the included references. It seems that the reader needs to have read the included references in order to fully understand the discussion.

Response:

Thank you for your comment. We have amended the healthcare disparities segment accordingly.

Changes to the Manuscript:

1. Healthcare disparities (Page 8, Lines 198-199 and Lines 221-240)
“Karamlou et al. studied 166,599 CHD admissions from 52 hospitals, of which 58,395 underwent congenital heart surgery and assessed whether interactions between SES and other patient and hospital factors could mitigate or potentiate adverse outcomes among this national cohort of patients

both with surgical and non-surgical CHD [15].”

“As to the interaction between race/ethnicity and SES in regionalization of CHD care in the context of the volume-outcomes relationship, we speculate that larger volume hospitals may perform better compared to smaller volume hospitals. The median total annual admission volume over our study period was 2,812 (IQR: 1,740-3,839); however, hospital population varied widely, with racial/ethnic composition and median neighborhood household income varying by hospital [15]. Alternatively, if the smaller volume hospital is in a geographically-diverse region and has evolved safety nets to resolve healthcare disparities, volume may no longer be an important determinant of outcomes among the socially disadvantaged or less prevalent ethnicities [15]. Further studies are needed to delineate whether modified care pathways have a causative relationship between prolonged length of stay and reduced mortality among black neonates. Additional population health initiatives and targeted resource allocation are needed to increase access for the vulnerable, disadvantaged racial and socioeconomic population to high-quality, multidisciplinary programs. Additional studies to decrease the healthcare access gap among the under-resourced, socially challenged, non-English speaking populations are warranted. Of note, a study by Woo et al. showed that infants with severe CHD who are publicly insured may need to increase their travel distance if they are restricted to seek care in-state solely; in other words, the study highlighted that receiving out-of-state care may mitigate access barriers to some and thus future regionalization efforts should take into consideration decreasing these access barriers particularly for the publicly insured infants [16].”

4. The mortality in Sweden was shown to be reduced after regionalization. Further discussion if these findings can be applied to a U.S. population would be interesting. In particular how the health care systems and distances might differ between countries. It is not clear if there are other examples of regionalization in other parts of the world?

Response:

We agree with this reviewer that some comparisons between the US and Sweden could add to the paper. We have provided some additional data that show differences between that country and ours, though this is limited by the limited number of centers in Sweden and the differences in healthcare coverage between both countries.

Changes to the Manuscript:

1. International Implications of Regionalization (Page 13, Lines 365-369 and Page 13, Lines 374-380)

“The centralization efforts in Sweden have resulted in longer travel distances for patients and their families, necessitating air transport more frequently; however, no increased risks of air transport were delineated compared to ambulance transport [8]. Centralization increased the annual number of pediatric heart operations from 550 to 620; of these, the percentage of open heart procedures increased from 60 to 79% [8].”

“Our theoretical model for congenital cardiac surgery delivery suggests that the US can be served by almost 100 fewer centers than what currently exists, with a decrease in median travel distance from 38.5 to 35.1 miles, and a theoretical median hospital volume threshold of 451 annual operations, augmenting favorable outcomes [4]. Both the Sweden and U.S. examples highlight the

positive volume-outcomes relationship; it should be noted nonetheless that these two countries have significant differences in their geography, number of centers and healthcare coverage infrastructure, making a head-on comparison imperfect.”

5. Overall, the topic of the manuscript is highly relevant. I would have liked a more thorough overview of the current literature with more in-depth discussion of actual numbers, limitations of the current/lack of studies and identification of future research areas.

Response:

Thank you for your comment. We have undergone a more extensive review of the literature, added a segment on the international state of congenital heart surgery with respective numbers, challenges facing regionalization and a segment on potential avenues for future research.

Changes to the Manuscript:

1. International State of Congenital Heart Surgery (Page 11, Lines 302-347)
2. International State of Congenital Heart Surgery (Page 12, Lines 298-344)

“The international arena of CHS regionalization is yet to be established. Given the significant gaps surrounding the availability of services and the varying factors influencing CHD outcomes in low-resource settings, it is helpful to assess the international landscape with a 30,000 foot view. Factors such as lack of cardiac surgery centers in several low- and middle- income countries, high cost of care and concomitant lack of insurance schemes capable of covering CHD repair services, lead to important hardships for families and patients [18]. These factors contribute to late case presentations; patients additionally present with comorbid conditions, making them particularly challenging to local teams not equipped with the knowledge and techniques to address them. Combined with limited resources and understaffing in existing centers [18], ensuring optimal outcomes in such low-resource settings is severely challenged.

In one study on CHD neonatal outcomes in Western India between 2009 and 2011, one significant predictor of mortality was incomplete repair of CHD lesions [19]. Other challenges discussed by the authors were late presentation of patients, with only 5% diagnosed in the antenatal stage [19]. Interestingly, mode of transportation, i.e. private versus transport ambulance did not impact mortality [19]. Furthermore, the total burden of CHS in India remains speculative, given the lack of national registries and an urgent need for them [20].

Other challenges facing CHS in low-resource settings include prolonged waiting time until surgery and paucity of human resources. In Thailand, median waiting time for pediatric patients referred for cardiac surgery was 195 days, with a 5% mortality at 2 years while waiting [21]. Such

phenomena are a threat to public health and attempts to resolve such challenges should ideally be made at the national level, in collaboration with international societies and experts. The paucity of human resources was highlighted in a survey of cardiac surgeons and residents in Nigeria, which showed the daunting need for pediatric cardiac surgery centers in the setting of a weak national health system, and poor human resources. Respondents emphasized the need for local and international partnerships with country leadership in hopes of advancing care for the pediatric population [22]. Such barriers emphasize the urgent need to focus attention on low-resource settings, to ensure timely and high quality access to CHS services.

Both the wealth of a nation and the size of its population contribute to the ability to provide specialized care. Five out of 58 small, developing island states, have only local health centers, which are dependent on and served by visiting surgeons. Aruba has no local cardiac surgery center, necessitating the state to send its cardiac patients abroad, costing it 12% of its total healthcare expenditure [23]. While itinerate surgeons provide a needed service, the model is unable to fill the needs of these nations.

Access to treatment for CHD in sub-Saharan Africa within two years of birth is <1% [24]. Nearly 300,486 infants are born annually in Africa with CHD [25]. Even though surgical palliation of functionally single ventricle patients can improve survival, children with these severe lesions have very poor care coverage in the African region because such care is expensive and therefore is not highly prioritized by policymakers from a cost-effectiveness perspective [26, 27]. Thus, ongoing education, collaboration with international societies, local civil society and policy makers is vital if progress in access to CHD surgical services is to be increased.

The global challenges discussed above demonstrate an urgent need for international collaboration between local CHD physicians, economic and ethnical experts to establish and/or advance access to CHS services within many burgeoning healthcare systems. The proposed structures, which should include centralization, will be variable and should be tailored to the needs of every country based on its national health system, population demographics, infrastructure, and insurance schemes used.”

3. International Implications of Regionalization (Page 13, Lines 379-388)

“An additional example of regionalization in a high-income country includes the Japan experience, which has demonstrated promise in the arena of regionalization. In its 2015-2016 status of cardiac surgery, the Japanese cardiovascular surgery database demonstrated that complex procedures, such as the Norwood, Rastelli and bidirectional Glenn were solely taking place at high volume centers. Despite this fact, complication rates, such as unplanned cardiac reoperation and phrenic nerve paralysis were still considerable, requiring further efforts for improvement [30]. Such data highlights that regionalization efforts hold promise, but require continuous monitoring to ensure the provision of the highest CHS quality possible for patients.”

4. Key Areas of Focus for Future Research (Page 14-15, Lines 427, 459)

“A clearer understanding of methods to curtail challenges faced by patients in low- and middle-income countries is needed. The full spectrum of CHS requires attention on several levels: timeliness of diagnosis, availability of modes of transportation, respective infrastructure, availability of resources, technical expertise, and the structure of postoperative surveillance. Situational analyses focused on these topics would be important in either the development of national healthcare delivery programs, or the modification of existing paradigms. Furthermore, data regarding the aforementioned areas and desired states should be coupled with a plan aimed at reforming overall health policy and governance structure within each country and region, as well as mechanisms to ensure accountability.

Coupling of these interests have been successfully used previously. It has been shown that further collaboration with political institutions is needed to advance the use of health evidence in policymaking [37]. In 2016, the World Society for Pediatric and Congenital Heart Surgery established its plan for international exchange of trainees to enhance international surgical education and treatment missions in addition to a potential system for global certification of its surgeons to facilitate movement of skill to areas of need [38]. Such plans are promising and future research efforts can potentially collaborate with global surgical technical experts to ensure that international efforts, such as the one announced by the World Society, are supported with the relevant expertise to set up local, national and regional capacity building mechanisms. Research could also focus on assessing the impact of such interventions and disseminating lessons learned to nearby regions or nearby countries in the same region. For example, the ‘Partnership for the Heart’ training initiative between Germany and Estonia demonstrated a 28% reduction in infant mortality secondary to congenital heart disease at 50% the cost incurred if the patients had to leave Estonia to seek care [39].

Multiple other areas of research also will be critical to understanding the impact of regionalization. Studying whether socioeconomic status and race are impacted adversely by regionalization, a potentially large challenge, are needed. Investigating the potential presence of an inflection point at which surgical volumes exceed the ability of a center to ensure top quality care, especially in low resource settings, where centers may have an excessive number of cases, will be important. The high volume of cases done in some LMIC will potentially facilitate the discovery of such an inflection point – although this will depend on the surrounding infrastructure to be evolved to a point where these systems can be compared to those of a developed country.”