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REVIEW

Paediatric kidney transplantation in under-resourced regions—a panoramic view

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Abstract

Kidney transplantation is the ideal choice of kidney replacement therapy in children as it offers a low risk of mortality and a better quality of life. A wide variance in the access to kidney replacement therapies exists across the world with only 21% of low- and low-middle income countries (LLMIC) undertaking kidney transplantation. Pediatric kidney transplantation rates in these under-resourced regions are reported to be as low as < 4 pmcp [per million child population]. A robust kidney failure care program forms the cornerstone of a transplant program. Even the smallest transplant program entails a multidisciplinary workforce and expertise besides ensuring family commitment towards long-term care and economic burden. In general, the short-term graft survival rates from under-resourced regions are comparable to most high-income countries (HIC) and the challenge lies in the long-term outcomes. This review focuses on specific issues relevant to kidney transplants in children in under-resourced regions by highlighting limitations in the capacity and health workforce, regulatory norms, medical issues, economic burden, factors beyond financial hardship and ethical considerations relevant to these regions. Finally, the perspective of strengthening transplant programs in these regions should factor in the bigger challenges that exist in achieving the health-related sustainable development goals by 2030.

Keywords Paediatric kidney transplantation · Low middle-income countries · Under-resourced regions · Developing nations · Challenges · Barriers · Outcomes

The ideal kidney replacement therapy

The choice of kidney replacement therapy for children with kidney failure should ensure a lower risk of morbidity and mortality and provide a better quality of life. In this regard, kidney transplantation is the ideal choice of kidney replacement therapy in children [1, 2]. Globally, in recent times, improved patient and graft survival have been observed with pre-emptive transplantation [3, 4]. Despite known advantages of living donor transplantation, with nearly 80% of living donors being parents of the child, the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) reveals that only one third of paediatric transplants arise from a living-related donor (LRD) [5]. Deceased organ transplant is beneficial to children in specific situations and in addition provides an opportunity for a potential second transplant with an LRD [4, 6]. While the world is striving to achieve the sustainable developmental goals (SDG) by 2030, child health care has taken centre stage. Investment towards achieving this goal has been proposed to be highly cost-effective in the long term [7], providing the unique opportunity to highlight various issues concerning the care of a child with kidney failure needing transplantation in low-resource settings.

Access to kidney transplantation

Amongst 215 countries across the globe, there are 82 countries which can be classified as low-middle- and low-income countries (LLMIC) [8]. These countries have a greater prevalence of chronic kidney disease (CKD) and death due to CKD in younger individuals (including adolescents) compared to high-income countries (HIC) on the global disease burden analysis [9].

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In addition, according to the Global Kidney Health Atlas, there is also a wide variation in access to kidney transplantation which is not available in 21% of countries (64% of African countries and 88% of LIC) [10, 11]. Kidney transplant rates in adults per million population (pmp) are 40.54 and 35.54 among HIC such as America and those in Europe, respectively, as shown in Fig. 1. In contrast, South-East Asian countries and those in Africa have the lowest rates of transplantation of 7.25 pmp and 1.33 pmp, respectively, and minimal deceased organ transplant activity in particular [12]. In Europe, rates of paediatric kidney transplants range from 0 to 13.5 per million children population (pmcp) [13]. Similar data for paediatric kidney transplants is very limited from LLMIC, some reporting rates of paediatric kidney transplantation as low as < 4 pmcp [14–16]. Moreover, the COVID-19 pandemic has added to the existing disparities in kidney transplantation rates across regions [12].

Even a small kidney transplant program demands a multidisciplinary workforce, high levels of expertise, and family commitment and an ability for patient follow-up with drug monitoring. Several gaps involving resource availability, capacity building, strategy development, and regulatory oversight exist in LLMIC. Across 32 countries in Europe, a strong association was observed between country income based on the GDP per capita and the rates of paediatric kidney transplantation. For every US$1000 increase in GDP per capita, the kidney transplant rate increased by 0.2 [13]. However, analysis of geographic measures of socioeconomic status from the United Nations Organ Sharing (UNOS) registry data revealed that socioeconomic status did not predict 1-year paediatric kidney transplant outcomes [17]. In LLMIC, in addition to economic disparities, access to transplantation to an extent is influenced by racial, ethnic and geographical disparities [18–20]. Similar observations have been reported from a country-wide study in Brazil. Among 271 paediatric kidney transplants from Brazil, disparities in access to transplants across various regions were related to large differences in health care resources and economic status within the regions [21].

Kidney failure care—the stepping stone

Outcomes in transplantation rely on a sound kidney failure care program. LLMIC have unique challenges regarding kidney failure care in adults [22] and children [23]. To a large extent, the status of kidney failure care in children depends on the standards of adult kidney care existing in the region. The real challenge that under-resourced regions or LLMIC face is prompt detection of CKD in children, early referral and providing optimal CKD 5D care services. The ground reality is that despite considerable progress in health care in recent years, the proportion of children presenting for the first time in late stages of CKD persists at around 25% over the last two

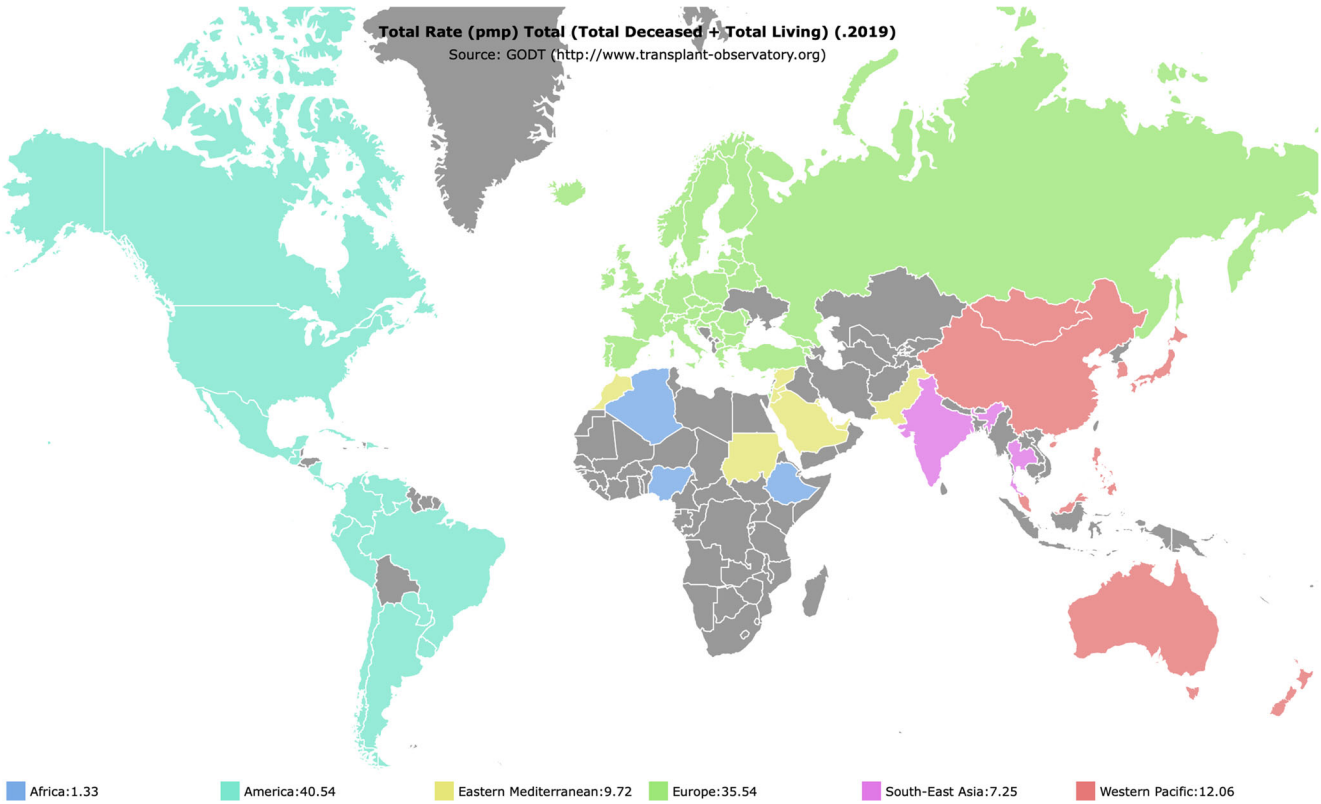

Fig. 1 Total rate (pmp) of kidney transplants undertaken across regions from the global database on donation and transplantation website

decades in India [24, 25]. Inequalities impact several steps in the overall process from diagnosis of kidney failure to receiving a transplant at country, institution and family levels [26].

Studies from a tertiary Indian centre report higher burden of CKD comorbidities and faster rates of CKD progression compared to HIC [25, 27]. Besides, an alarming observation from the same centre included a significant (42%) proportion of children with CKD 5 being lost to follow-up with discontinuation of care while only 20% underwent transplantation [28]. In resource-limited settings, many of these children present late with life-threatening complications or CKD 5 requiring urgent dialysis that makes pre-emptive transplantation impractical. These situations demand optimal resources, infrastructure and availability of trained health personnel [29, 30]. On a positive note, parental acceptance of manual chronic peritoneal dialysis especially in younger children in resource-constrained settings is improving, which may pave the way for transplantation in younger children and infants in these regions [31, 32].

To facilitate better preparation for and to maximise sustainability of kidney replacement therapies in areas with resource-limited regions, the International Society of Nephrology (ISN) is developing guidance documents applicable to both adults and children for the World Health Organisation. A recent review addresses the various components involved in incorporating transplantation within integrated care for kidney care [33]. From a national level perspective, the key areas governing sustainable transplant services include legislation, regulation, health finance, health workforce, family and community involvement, maintenance of registries, strengthening deceased organ transplant programs and abiding by ethical standards. The essential components needed for a sustainable transplant program at specific levels of health care are depicted in Fig. 2.

Dearth of national registries

A major limitation that needs to be addressed regarding priorities is the lack of national registries for CKD 5, dialysis or kidney transplantation in the majority of under-resourced nations. The paucity of comprehensive health information systems curtails the potential to capture critical information on the burden, needs and provision of kidney replacement therapies including transplantation in these regions. Adult transplant registries exist in 44% of LMIC and none in LIC [10, 11]. In fact, populous nations like India and Germany, and parts of Africa, do not have a registry for kidney transplantation [34]. However, countries like Brazil, Thailand and South Africa have made appreciable progress by establishing paediatric kidney transplant registries [35–37]. The various dimensions and utility of registry data as a source of evidence beyond randomised controlled trials have been well discussed with regard to kidney and liver transplantation [38]. Registry management needs to be staffed by a committee that involves all

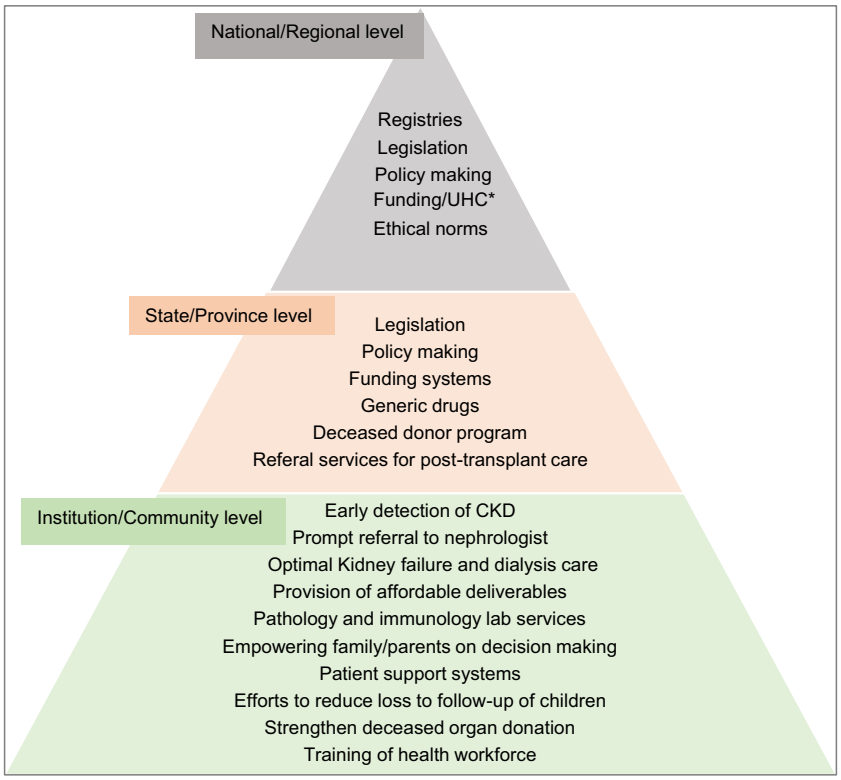

Fig. 2 Essential components of a sustainable paediatric transplant program at various levels of health care relevant to LLMIC based on reference 33. *Universal health coverage

stakeholders who ensure mandatory reporting, provision of adequate technology infrastructure, human workforce and sources for funding. Voluntary participation is the norm for most national registries which requires extensive "buy-in" with ongoing motivation and is most often governed by national societies or bodies rather than the government. Data collection can be a significant challenge but new electronic databases available on smart phone technology have made this easier.

Transplant outcomes in LMIC

The updated NAPRTCS data (2012–2017) reports graft survival rates at 1 year, 3 years and 5 years of 99.5%, 97.2% and 94.9% in living donor transplants and 97.6%, 94.4% and 90.1%, respectively, in deceased donor transplants [4]. The allograft survival rates from LLMIC are depicted in Table 1 [15, 39–55]. Though the 1-year allograft survival rates are quite similar to the NAPRTCS report, the outcomes at 5 years and beyond pose major concerns in these countries. Key factors associated with graft loss have been deceased donor transplant (with resultant increased cold ischaemic times and "less than perfect" older donors), invasive infections, cytomegalovirus disease and more than two rejection episodes, with sepsis being the key contributor to patient loss [41, 43–56]. The unfortunate event of patient loss with an underlying functional allograft is not an uncommon scenario. Predictors of chronic rejection are secondary to poor compliance, lack of induction therapy and multiple episodes of acute rejection [44]. Access to support services, including transplant histopathology, monitoring of viral load and drug level, access to vaccines, imaging and immunology tests are limited in most LLMIC that contribute to suboptimal outcomes [57]. Adolescent patients often fall between services and adolescent care is a challenging field especially in under-resourced regions. Planned transition and development of specific adolescent clinics with age-appropriate treatment and psychological support improve engagement with health services and ultimately improve compliance. This is really important for resource-limited adult services [58].

Most LLMIC initiate transplant services through a living related donor program. Development of a deceased donor program is challenging in the developing world as it demands changes in legislation (brain death legislation), better infrastructure, community involvement, support from intensive care teams, rapid turn-around of transplant immunology services and interventions to address educational, social and religious barriers to organ donation. Currently of 54 countries in Africa, only 4 have brain death legislation (South Africa, Tunisia, Egypt and Sudan). Besides, due to a huge demand for organs amongst adults, there is resistance to enforcing prioritised allocation criteria for children in these regions, leading to prolonged waiting periods for children and adolescents. This often leads to poor growth and failure to thrive with developmental delay and chronic issues of rickets and anaemia. There needs to be a visionary move towards paediatric recipients receiving solid organs from paediatric deceased donors, which is currently not a practice even in the best of centres in LLMIC countries. Deceased donor donation has been the predominant approach to transplanting in children in countries like South Africa (58%), Chile (61%), Saudi Arabia (56%) and Brazil (32%) with limited data available from other LMIC [48, 59]. Thailand reported a comparable 5-year graft survival between children receiving living related and deceased donor transplants [48]. An Indian study of 37 children who received deceased donor kidney transplants at a government institution demonstrated 1-year, 5-year and 10-

Table 1 Kidney graft survival of live related transplants in LLMICs

Country-wise published data	Graft survival % (LRD)			
	1 yr	5 yr	10 yr	15 yr
Brazil [39]	90	72	59	
South Africa [40]	82	44	23	
India [41–47]	90–98	80–92	66–85	77.6% (1 centre)
Pakistan [15]	96	81	-	
Thailand [48]	100	86	-	
Iran [49]	90	81	62	
Chile [50]	87	78	-	
Egypt [51]	93	73	-	
Turkey [52]	91	67	-	
Jordan [53]	97	91 (3yr)	-	
Saudi Arabia [54]	98	92	-	
Kuwait [55]	98	-	84	

year graft survival rates of 90.4%,73.3% and 73.3%, respectively [60]. A public-private partnership model for a sustainable donor pool program relevant to developing countries has been set up by the Multi Organ Harvesting and Networking (MOHAN) foundation (http://www.mohanfoundation.org/), a philanthropic non-governmental organization aiming to promote organ donation and transplantation in India. Empowerment of trained transplant coordinators by the foundation led to an appreciable increase (65%) in the willingness among families of the deceased to donate organs [61]. Appointment of paediatric transplant co-ordinators can also increase the donation rate in children's health care facilities.

Medical issues

Native kidney diseases that are known to recur post-transplant, those that warrant genetic testing and those that need combined kidney-liver transplantation pose challenges to paediatric nephrologists in LLMIC. A multi-centre prospective study in 308 children with CKD 5 from the UK observed that barriers to transplantation included disease-related factors in 36%, donor unavailability in 27% and size of the child in 20% [62]. A retrospective study of 155 children with CKD 5 from a single LMIC centre revealed non-medical barriers to overshadow medical issues [28]. The medical issues included lack of timely access to deceased donor organs, incomplete bladder preparation among those with urological issues and lack of expertise with multi-organ transplantation as well as lack of expertise in managing transplantation in small children and infants.

Variable outcomes in children transplanted with lower urinary tract dysfunction have been reported from few LMIC, where specific concerns regarding repeated urinary infections, poorer long-term graft function and the need for frequent urological interventions are described [41, 63–65]. An interim analysis of transplanted children with (n = 23) and without abnormal lower urinary tract problems (n = 52) from the Department of Pediatric Nephrology, St John's Medical College Hospital, revealed suboptimal long-term graft function [94%, 87%, 68% vs. 94%, 90%, 86%] and patient survival [100%, 84%, 65% vs. 98%, 91%, 91%] at 1 year, 5 years and 10 years, respectively (unpublished data).

Poor growth post-transplant has been a common concern with steroid sparing or avoidance protocols not being followed [44]. In the developed world, a reduction in cardiovascular and infection-related deaths has led to improved survival after paediatric kidney transplantation [66]. A recent study from an LMIC reported a high burden of masked and nocturnal hypertension in paediatric transplant recipients [67].

The spectrum of infections described in children post-transplant includes urinary tract infections, sepsis, pneumonia, tuberculosis, meningitis and viral infections [44, 68]. Infections were noted in 50% of children post-transplant while sepsis/severe infections contributed to two-thirds of deaths [44]. Death with graft function is common and occurs secondary to sepsis or severe infections among the majority of adults post-transplant [69]. With limited access to molecular diagnostic tests such as real-time polymerase chain reaction, nucleic acid tests and multiplex ligation-dependent probe amplification, the diagnosis of viral infections is delayed causing child morbidity and graft dysfunction. Therapies for viral disease are expensive, further compromising the social and economic security of families.

Capacity and health workforce

A survey of paediatric kidney transplant practices in India highlights the key concerns that are applicable to LMIC. In stark contrast to well-resourced nations, transplantation in children in the majority of centres was undertaken by adult nephrologists (61%) with greater numbers being done in private hospitals [70]. However, most transplants in children undertaken by adult nephrologists include a body weight of 20 kg and above. A skillful transplant surgeon is indispensable for a successful transplant, to the extent that in some LLMIC centres, there is dependence on transplant surgeons from overseas to facilitate the transplants. Enhancing workforce capacity through training of nurses in transplant and critical care nursing, having paediatric transplantation made mandatory in the curriculum for post-doctoral training and including medical social work services within the framework of multidisciplinary teams are some key steps to strengthen the workforce. A structured and collaborative approach between paediatric and adult nephrologists for transition of adolescents to adult renal services is lacking in most well-established centres.

In many countries in South Asia, public/government hospitals receive a large number of children with CKD and CKD 5 but many are unable to provide kidney replacement therapies for children in particular. Private centres that have the expertise and infrastructure in place have to shoulder the burden of raising funds and cutting costs to make kidney replacement therapies including transplantation affordable to all sectors of society. An example of a public-private partnership model to cater to providing kidney transplant to poorer sectors of society in a LMIC is described for adults [71].

Most successful private specialty hospitals are located in metropolitan cities and some have geared up to perform highly specialised transplant-related procedures like ABO incompatibility and paired organ donation in children [72, 73]. However, a paediatric ABO-incompatible kidney transplant has also been reported from a university teaching hospital in Nepal [74]. The hard fact remains that families belonging to lower-middle and lower socioeconomic segments of society struggle to cope with the challenges of preparing their child

for transplantation, sustaining long-term expenses, maintaining close follow-up and transition of care of their children to adult service.

Economic barriers

The most important barrier to transplantation in LLMIC is the high costs involved. The concept that transplantation is not as expensive as long-term dialysis has been proven in adults but can be applied to children as well [75].

Table 2 demonstrates the approximate costs related to paediatric dialysis and transplantation from two centres in LLMIC. We observe a tendency for families to agree to some form of dialysis as an approach to manage the crisis of kidney failure. This happens more so due to children presenting late and needing emergent kidney replacement therapy. Most families thereafter continue with long-term dialysis for several reasons despite being cognizant of the fact that expenditure towards long-term dialysis exceeds that of transplantation. Without the support of insurance, families face out-of-pocket costs that can lead to catastrophic expenditures from any modality of kidney replacement therapy, leading to graft loss in case of transplantation [76, 77]. Public funding for kidney replacement therapy exists in most HIC but is minimal in LLMIC. The need for urgent funding support towards kidney transplantation in children has been recently highlighted in a study from Nigeria [78]. Though some LMIC are providing funding models for dialysis, there is no such support for transplantation as yet [79]. While LLMIC countries are moving towards universal health care, from a policy-making perspective, it becomes important to assess the feasibility and benefits involved in supporting dialysis or transplantation within regions [80]. Maintenance immunosuppression adds to the financial burden of transplantation and a transition from brand to generic drugs could cut costs of life-long therapy [81]. A community-government partnership model for funding paediatric kidney replacement therapies has been implemented in Pakistan [15].

Barriers beyond financial hardship

Commuting from rural and remote areas to reach tertiary hospitals has been a major concern observed in developing nations for both pre- and post-transplant long-term care [14, 15]. As an example, from a community perspective in India, basic kidney function testing is not done in a village centre or a subcentre. Travel distance to the nearest primary health centre that cares for a population of 20,000–30,000 and has the facility to test for kidney function ranges from 5 to 10 km and travel to a district hospital for imaging studies may reach 35 km [82]. Moreover, substantial variability in serum creatinine assays exists in laboratories across levels of health care.

Barriers to accomplishing transplant in an under-resourced setting includes the unique issue of loss to follow-up or disappearance of children and their families from the treatment centre [28]. This is associated with low socioeconomic status, longer time and distance to travel, parent's education and parent's occupation. Negative attitudes towards transplantation and organ donation among parents and families are also encountered. Lack of interest in transplantation was observed in 61% which included reasons like the father being unwilling to pursue transplantation, focus on the birth of the next child, hope that kidney failure will recover miraculously and competing family health issues. Another issue seen in 15% was neither parent being fit or willing to donate and unwilling to miss work as daily wage labourers. A qualitative study of children and adolescents found that negative emotions regarding transplantation among children and adolescents included

Table 2 Approximate costs related to paediatric kidney replacement therapies from two centres belonging to LMIC

Kidney replacement therapies for a child	India[a] Cost (USD ex rate = 69) Rounded to nearest USD	South Africa[b] USD Government subsidised
Maintenance dialysis monthly		
CAPD costs (2 bags dialysate + medications + clinic visit)	489	650
HD (3 per week) + medications + clinic visit)	311	450
Transplant-related treatment		
Cost of LRD transplantation	9420	10,800
Monthly immunosuppression	145	390
Monthly transplant clinic visit	51	150

USD United States Dollar, *CAPD* continuous ambulatory peritoneal dialysis, *HD* hemodialysis

[a] St John's Medical College Hospital, Bangalore—a non-government, "not for profit" academic Institution

[b] Red Cross War Memorial Children's Hospital, University of Cape Town–Government hospital

fear, anxiety, guilt for burdening siblings and parent as donors [83]. Children and adolescents did view kidney transplantation as freedom from dialysis while knowing that transplantation is not necessarily a return to full health.

Ethical issues

It is imperative to consider equity in the provision of kidney replacement therapy in LLMIC and this is governed by factors like availability of resources, affordability of treatments and acceptability concerning ethical and societal standards [84]. Issues regarding unregulated organ trade and transplant tourism prevail in these regions [14, 85, 86]. Gender disparities have been recognised with respect to donors and recipients across LMIC [87, 88]. A pragmatic and critical ethical issue is consideration of family resources while making medical recommendations for transplantation (an expensive treatment with no guarantee of success) to a child belonging to a poor family. This discussion includes consideration of principles of beneficence, maleficence, justice and autonomy [89]. A preliminary guidance document on the ethical framework and approach to ethical challenges in kidney failure care, including kidney replacement therapies, has been developed for LMIC but requires further refinement [90].

Steps towards bridging gaps

Legislation (regarding donors and recipients), regulatory norms, policy advocacy at local hospitals and government departments at health care levels for both children and adolescents, registries, health financing, adherence to ethical standards and community and patient engagement are the key domains that under-resourced nations need to work on to build effective transplant programs. Templates for development of transplant programs as a component of integrated kidney failure care in LLMIC have been put forth by the ISN [33].

Scientific bodies such as the ISN, The Transplantation Society (TTS), the International Pediatric Nephrology Association (IPNA), the International Society of Peritoneal Dialysis (ISPD) and the International Pediatric Transplant Association (IPTA) have invested in unique exchange training programs and educational collaborations. These initiatives have gone a long way in empowering under-resourced countries to undertake transplantation in both adults and children with an additional responsibility of engaging in efforts to solve regional challenges. An example of a collaboration that not only reflects the strengths of collaboration but also projects the specific challenges relevant to an under-resourced region is a centre in Myanmar. A centre in Yangon Hospital, Myanmar, undertook the first paediatric transplantation under the umbrella of the ISN Sister renal centre collaboration in

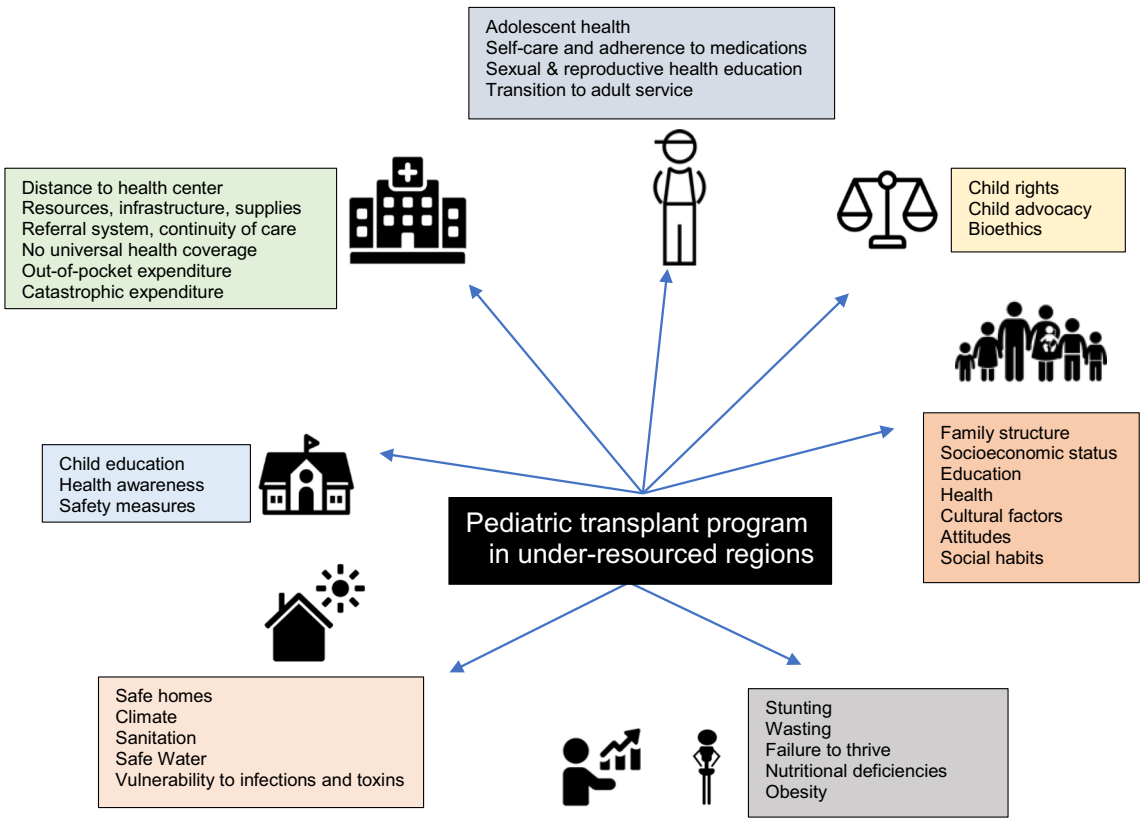

Fig. 3 Components of health-related SDG that potentially impact paediatric transplantation in under-resourced regions [7, 87]

2017. Under the guidance and mentorship of the team from Children Kidney Centre, National University Hospital, Singapore, kidney failure care services were implemented, pre-transplant preparation was undertaken and ten children received transplants successfully. Key challenges noted were convincing the community and medical fraternity about the need for and feasibility of undertaking transplantation in children, raising funds for the surgery, supporting post-transplant immunosuppression and dealing with various issues of sustaining follow-up care. Medical professionals had to shoulder responsibilities beyond the purview of nephrology care through home visits, ensuring basic water supply, housing and sanitation for the children following transplantation (personal communication with Prof. Yi Yi Khin, Pediatric Nephrologist, Myanmar).

This brings us back to reality. If we take a step back from the transplant scene, we see a panoramic view of the under-resourced world that is faced with very basic and complex challenges related to health. Figure 3 illustrates the various health-related SDGs that pose challenges to kidney failure care and transplantation in under-resourced regions. The under-resourced world in particular is battling against health-related SDGs like maternal, neonatal and under-five mortality, striving to find ways to deal with a huge burden of basic needs like clean water supply, sanitation hygiene, safe homes and other environmental hazards towards the timeline of 2030 [7, 91, 92]. In this context, it becomes crucial to understand and accept the fact that unless progress towards solving these elementary issues and inequalities impacting child health takes place with the required momentum, kidney failure care and kidney replacement therapies will continue to remain a big challenge in under-resourced regions. However, on a brighter note, as it demands a multidisciplinary approach, development of transplant programs in under-resourced regions will have positive influences on the entire health care system, serving as an impetus to develop and sustain higher standards of health care at all levels in the region.

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Declarations

Conflict of interest The authors declare no competing interests.

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