Global Surgery Bootcamp Module 7 – Cleft Lip and Palate

Learning Objectives

- Explain what orofacial cleft is, and how and why it develops
- Draw connections between global surgery, global burden of disease, and congenital anomalies (particularly orofacial cleft)
- Articulate how Operation Smile's work fits within the Global Surgery space
- Identify barriers to care for people living with orofacial cleft, and barriers for Operation Smile patients in particular
- Identify benefits and drawbacks of the short-term mission model for care delivery

Materials

Read

1. Mossey, "Cleft lip and palate" (pages 2-14)
2. Sitkin, "Congenital Anomalies in low- and middle-income countries: the unborn child of global surgery" (pages 15-19)
3. Sitkin, "Congenital anomalies in the context of global surgery" (pages 20-23)
4. Carlson, "Inequitable access to timely cleft palate surgery in low- and middle- income countries" (pages 24-29)
5. Swanson, "Patient barriers to accessing surgical cleft care in Vietnam" (pages 30-41)
6. Yao, "Barriers to reconstructive surgery in low and middle income countries a cross sectional study" (pages 42-50)
7. Stewart, "Cleft-related infanticide and abandonment: a systematic review" (pages 51-57)
8. Carlson, "A health systems perspective on the mission model for cleft lip and palate surgery" (pages 58-62)

Watch

9. Module 7 "Cleft Lip and Palate" Summary Video

Things to Think About

1. Global Surgery is an incredibly broad concept. How/where does Operation Smile's work fit within that space?
2. What barriers to care do patients in need of surgery experience? Do people with cleft conditions have the same or different barriers?
    a. Do you think Operation Smile patients experience a different set of barriers compared to what patients with cleft in the United States or Europe experience? Why or why not?
3. Do you believe surgical charities have a role to play in the global surgery conversation? Why or why not? If yes, what is the role?
4. There is a lot of talk in global health about "sustainability" (reference 1, reference 2). What does sustainability mean to you? Would you classify Operation Smile's work as sustainable? Why or why not?

Cleft lip and palate

Peter A Mossey, Julian Little, Ron G Munger, Mike J Dixon, William C Shaw

Clefts of the lip and palate are generally divided into two groups, isolated cleft palate and cleft lip with or without cleft palate, representing a heterogeneous group of disorders affecting the lips and oral cavity. These defects arise in about 1·7 per 1000 liveborn babies, with ethnic and geographic variation. Effects on speech, hearing, appearance, and psychology can lead to longlasting adverse outcomes for health and social integration. Typically, children with these disorders need multidisciplinary care from birth to adulthood and have higher morbidity and mortality throughout life than do unaffected individuals. This Seminar describes embryological developmental processes, epidemiology, known environmental and genetic risk factors, and their interaction. Although access to care has increased in recent years, especially in developing countries, quality of care still varies substantially. Prevention is the ultimate objective for clefts of the lip and palate, and a prerequisite of this aim is to elucidate causes of the disorders. Technological advances and international collaborations have yielded some successes.

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Introduction

Non-syndromic orofacial clefts, which include cleft lip, cleft lip and palate, and cleft palate alone, comprise a range of disorders affecting the lips and oral cavity (figure 1), the causes of which remain largely unknown. Effects on speech, hearing, appearance, and cognition can lead to long-lasting adverse outcomes for health and social integration.

Affected children need multidisciplinary care from birth until adulthood and have higher morbidity and mortality throughout life than do unaffected individuals.[1,2] Findings of studies have shown an increased frequency of structural brain abnormalities[3] and that many children and their families are affected psychologically to some extent.[4] Although rehabilitation is possible with good quality care, orofacial clefts inevitably pose a burden to the individual, the family, and society, with substantial expenditure in terms of health and related services.

Care for children born with these defects generally includes many disciplines—nursing, plastic surgery, maxillofacial surgery, otolaryngology, speech therapy, audiology, counselling, psychology, genetics, orthodontics, and dentistry—but it forms only a part of the clinical load of every area, meaning that care has tended to be fragmented. This fragmentation of care has led to substantial variations in management, which continue to cause controversy. Furthermore, in both developing and developed countries, standards of care for patients with cleft lip, cleft lip and palate, or cleft palate alone remain a cause for concern.[5]

Developmental pathogenesis

Development of the lip and palate entails a complex series of events that require close coordination of programmes for cell migration, growth, differentiation, and apoptosis. Neural crest cells, which delaminate from the neural folds, contribute to and migrate through mesenchymal tissue into the developing craniofacial region where, by the 4th week of human embryonic development, they participate in formation of the frontonasal prominence, the paired maxillary processes, and the paired mandibular processes, which surround the primitive oral cavity. Formation of the nasal placodes (ectodermal thickenings) by the end of the 4th week of embryogenesis divides the lower portion of the frontonasal prominence into paired medial and lateral nasal processes. By the end of the 6th week of development, merging of the medial nasal processes with one another and with the maxillary processes on each side leads to formation of the upper lip and the primary palate. Immediately before completion of these processes, the lateral nasal process has a peak of cell division that renders it susceptible to teratogenic insults, and any disturbance in growth at this critical time can lead to failure of the closure mechanism.[6]

The first sign of overt development of the secondary palate happens during the 6th week of embryogenesis with outgrowth from the maxillary processes of paired palatal shelves, which initially grow vertically down the sides of the developing tongue. During the 7th week of development, the palatal shelves rise to a horizontal position above the tongue and come into contact and fuse

Search strategy and selection criteria

Our search strategy was formulated to identify any meta-analyses and previous systematic reviews in all aspects of orofacial cleft treatment, palatogenesis, and cleft cause and pathogenesis, in addition to all published cohort studies (and where appropriate, comparison groups) and case-control studies. We searched the Cochrane Library, Medline (via PubMed, Internet Grateful Med, OVID, and Knowledgefinder), HealthSTAR, POPLINE, SDILINE, SPACELINE, Embase, OLDMEDLINE, CINAHL, and ASKSAM with a combination of keywords: 'genetics', 'gene-environment interaction', 'risk factors', 'maternal', and 'cleft lip'. A so-called grey literature search was done via the ECHHSR (European Clearing House on Health Systems Reform), and we consulted the UK National Research Register Database to identify any current and unpublished relevant studies. The reference lists and bibliographies of all previous publications were scanned to find any publications not already identified by our electronic search strategy.

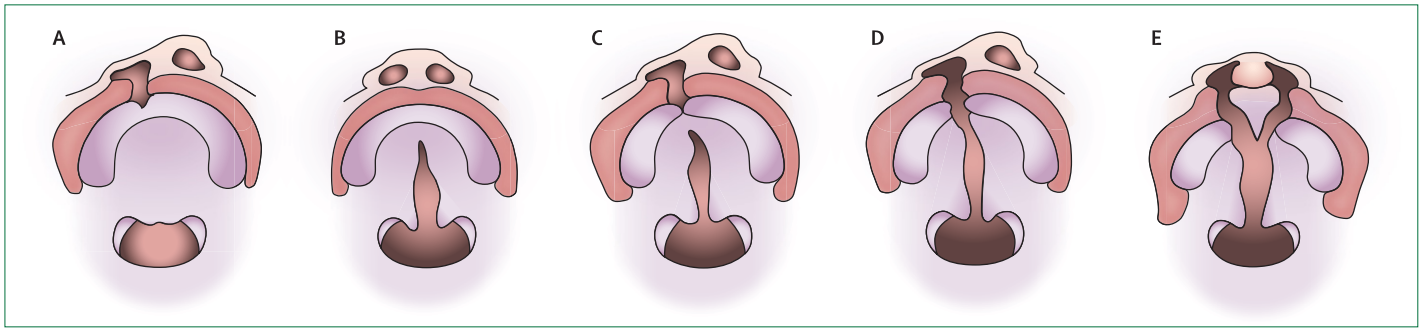

Figure 1: **Non-syndromic orofacial clefts**
(A) Cleft lip and alveolus. (B) Cleft palate. (C) Incomplete unilateral cleft lip and palate. (D) Complete unilateral cleft lip and palate. (E) Complete bilateral cleft lip and palate. Reprinted with permission from: Shaw WC. Orthodontics and occlusal management. Oxford: Butterworth-Heinemann, 1993.

to form a midline epithelial seam, which subsequently degenerates to allow mesenchymal continuity across the palate. The palatal mesenchyme then differentiates into bony and muscular elements that correlate with the position of the hard and soft palate, respectively. In addition to fusing in the midline, the secondary palate fuses with the primary palate and the nasal septum. These fusion processes are complete by the 10th week of embryogenesis; development of the mammalian secondary palate thereby divides the oronasal space into separate oral and nasal cavities, allowing mastication and respiration to take place simultaneously.[6]

Since the lip and primary palate have distinct developmental origins from the secondary palate, clefts of these areas can be subdivided into cleft lip with or without cleft palate and isolated cleft palate in which the lip is not affected. This subdivision is validated by the finding that, under most circumstances, cleft lip with or without cleft palate and isolated cleft palate do not segregate in the same family.[7] Integration of findings of human genetic studies (including positional cloning strategies, parametric-based genetic linkage analysis, non-parametric affected sib-pair approaches, chromosomal analysis, and candidate gene-based association studies) with data of experimental embryological techniques in model organisms has increased our knowledge of both the fundamental mechanisms driving normal facial morphogenesis and how these are disturbed in cleft lip with or without cleft palate and isolated cleft palate.

Mice and chicks have played a central part in dissection of the molecular pathways underlying development of the lip and palate.[8] In both species, development of the lip and primary palate closely parallels that seen in human beings, with facial processes visible at embryonic day (E) 9·5 in mice (stage 19 in chicks) and the upper lip becoming continuous by E11·5 in mice (stage 28 in chicks). Because the embryonic chick face is readily accessible for experimental manipulation and will continue to develop after such interventions in the egg, much of our knowledge of development of the lip and primary palate is derived from analysis of this species. The available evidence, however, suggests that similar, if not identical, mechanisms operate in mice and human beings.

In this context, molecular studies have shown that initiation and outgrowth of the facial processes and specification of their identity is controlled, at least partly, by interaction of fibroblast growth factors, sonic hedgehog (SHH), bone morphogenetic proteins, the homeobox-containing genes *Barx1* and *Msx1*, the distal-less homeobox-containing (*Dlx*) genes, and local retinoic acid gradients.[9–12] By contrast, although fusion events that contribute to formation of the lip and primary palate seem to entail a combination of apoptosis and epithelial-mesenchymal transformation, their molecular control has been studied less extensively. These events are, however, thought to include: SHH; MSX1 and MSX2; and control of signalling by bone morphogenetic proteins and fibroblast growth factors in part by *TP63*—the gene mutated in the allelic disorders ectrodactyly, ectodermal dysplasia, and clefting syndrome and ankyloblepharon, in which cleft lip with or without cleft palate and isolated cleft palate are defining features.[11,13,14]

Conversely, our knowledge of development of the secondary palate has been derived to a much greater extent from analyses of mice, in which morphological events are essentially the same as those happening in human beings, with the palatal shelves initiating from maxillary processes on E12 and growing vertically, lateral to the tongue, on E13.[15] At this stage, each palatal shelf consists of a central core of mesenchyme derived from neural crest cells surrounded by a simple undifferentiated epithelium, comprising a basal layer of cuboidal cells covered by a layer of flattened periderm cells.[16] Molecular control of palatal shelf initiation and vertical growth is thought to entail complex signalling cascades with transcription factors and growth factors and their receptors, including *Osr2*, *Lhx8*, *Msx1*, *Fgf10*, *Fgfr2b*, *Tgfb2*, and *Tgfbr2*.[15] Signalling between the palatal epithelium and mesenchyme is known to have a key role in regulation of palatal growth—eg, fibroblast growth factor 10 (FGF10) signals from the palatal mesenchyme to its receptor FGFR2b, which is expressed in the palatal epithelium. Loss of function of either FGF10 or FGFR2b

causes a reduction in mesenchymal proliferation and an increase in apoptosis, leading to truncation of the palatal shelves.[17] Importantly, activation of FGFR2b by FGF10 is crucial for maintenance of SHH expression in the palatal epithelium: loss of SHH function in this tissue also leads to cleft palate.[17] Signalling between the epithelium and mesenchyme during palatal growth has also been shown between *Msx1*, *Bmp4*, *Shh*, and *Bmp2*; *Msx1* regulates expression of *Bmp2* and *Bmp4* in the mesenchyme and *Shh* and *Bmp4* in medial edge epithelium. In turn, *Shh* stimulates *Bmp2* expression in the mesenchyme, which regulates growth of the palatal shelves.[18] A loss-of-function mutation in *MSX1* has been reported in a patient with cleft lip and palate.[19]

At a precise developmental stage (E14·5), the palatal shelves rapidly move to a horizontal position above the dorsum of the tongue and come into contact. Palatal shelf elevation is thought to be driven by regional accumulation and hydration of glycosoaminoglycans, mainly hyaluronic acid, which provides an intrinsic shelf force, directed by components of the extracellular matrix and local epithelial changes, within a permissive environment provided by differential head growth.[15] Another factor that is important to ensure that the palatal shelves rise correctly is control of competence for oral and palatal shelf adhesion. This mechanism must be regulated precisely so that vertical palatal shelves are adhesion-incompetent while they are in close contact with other structures but once they are raised above the tongue they rapidly acquire adhesion capability if they are not to remain cleft. Control of periderm differentiation by the membrane-bound signalling molecule jagged 2 (JAG2) is important in this process.[20] Another factor central to this process is interferon regulatory factor 6 (IRF6)—the protein encoded by the gene mutated in the allelic disorders van der Woude's syndrome and popliteal pterygium syndrome, which are characterised by varying degrees of cleft lip with or without cleft palate, isolated cleft palate, lower lip pits, hypodontia, and epidermal and genital anomalies.[21–23]

Once the palatal shelves have risen they must adhere and fuse; although only partly characterised, palatal fusion seems to be driven by several cell-adhesion molecules (including nectin 1) and desmosomal components[24,25] and growth factors including transforming growth factor α (TGFA) and epidermal growth factor receptor (EGFR)[26] and members of the transforming growth factor β superfamily—eg, TGFβ3 is essential in these processes. Findings of expression analyses initially indicated that TGFβ3 is expressed specifically in future medial edge epithelium at E13 before palatal shelf elevation and in the medial edge epithelium itself at E14·5, suggesting an important role for this molecule in palatal fusion.[27] This hypothesis is supported by demonstration that ablation of the gene in vivo prevented palatal fusion and that the adverse effect of ablation could be rescued by administration of exogenous TGFβ3.[28,29] Data from subsequent developmental studies have suggested that TGFβ3 might promote palatal fusion via synergistic effects—by stimulating initial adhesion of the palatal shelves, increasing the surface area of the medial edge epithelium through induction of cellular bulges and filopodia, and by promoting degeneration of medial edge epithelium.[29–33] At the molecular level, TGFβ3 has been shown to regulate members of the matrix metalloproteinase family, including TIMP2 and MMP13, which have been implicated in proteolytic degradation of the extracellular matrix.[34] IRF6 is downregulated in the medial edge epithelium of mice with mutations in *Tgfb3* and *Tgfbr2*, which suggests strongly that IRF6 lies downstream of TGFβ3 signalling for the fate of medial edge epithelium.[35,36]

Once the palatal shelves have come into contact and the medial epithelial seam has formed, the seam must degenerate to allow mesenchymal continuity across the palate. Detection of dead or dying epithelial cells together with identification of activated cells positive for caspase 3 and TUNEL (terminal deoxynucleotidyl transferase nick-end labelling) in the disintegrating medial epithelial seam indicates that apoptosis has a key role in seam degeneration.[37] Further evidence for this hypothesis is derived from analysis of palatal development in mice without apoptotic protease-activating factor 1. In these mutant mice, palatal shelf adherence happens normally but the medial epithelial seam does not degenerate.[38] The issue of whether medial epithelial seam cells undergo epithelial-mesenchymal transformation remains controversial, but evidence is emerging that substantial epithelial-mesenchymal transformation does not take place;[36] rather, a subset of medial epithelial seam cells seem to migrate to the oral and nasal surface of the palate where they form triangular areas of epithelial cells.[39] Importantly, if the migration of periderm cells is prevented, these triangular regions fail to form; thus, periderm cells must migrate out of the medial epithelial seam to the epithelial triangular areas to allow fusion to take place. Subsequently, the epithelium on the nasal aspect of the palate differentiates into pseudo-stratified, ciliated columnar cells, and tissue on the oral side changes into stratified, squamous, keratinising cells. Although epithelial differentiation is specified by the underlying mesenchyme,[15] the molecules shaping the fate of the oral and nasal epithelia are unknown.

Descriptive epidemiology

The birth frequency of cleft lip, cleft lip and palate, and cleft palate alone is not known in some parts of the world. In many regions for which information is available, differences in sample source (hospital *vs* population), duration, method of ascertainment, inclusion criteria, and sampling fluctuation restrict comparability.[40] Overall, available findings indicate that orofacial clefts arise in about 1 in 700 livebirths.[41] International data from 57 registries for 1993–98 suggest a variation in prevalence

at birth of cleft lip with or without cleft palate of 3·4–22·9 per 10 000 births, and an even more pronounced variation for isolated cleft palate, with prevalence of 1·3–25·3 per 10 000 births (figure 2).[41] Differences in methods of ascertainment might have a greater effect on isolated cleft palate than on cleft lip with or without cleft palate, because cleft palate is less noticeable externally. Rates of cleft lip with or without cleft palate were high in parts of Latin America and Asia (China, Japan) and low in Israel, South Africa, and southern Europe. Rates of isolated cleft palate were high in Canada and parts of northern Europe and low in parts of Latin America and South Africa. Comparisons between ethnic groups within the USA[42] and the UK,[43] and studies of immigrants to the USA from Japan and China,[42,44] indicate that migrant groups have rates of cleft lip with or without cleft palate closer to those of the area from which they originated than those in the area into which they have moved.

In combined data from European registries for 1995–99, 3·5% of babies with cleft lip with or without cleft palate were stillborn and 9·4% were from terminated pregnancies; respective proportions for isolated cleft palate were 2·4% and 8·1%. No consistent time trends[45] or seasonal patterns[46,47] in prevalence at birth of either defect have been recorded.

Cleft lip with or without cleft palate is most frequent in males, and isolated cleft palate is most typical in females, across various ethnic groups; the sex ratio varies with severity of the cleft,[40] presence of additional malformations, number of affected siblings in a family, ethnic origin, and possibly paternal age.[41] In white populations, the sex ratio for cleft lip with or without cleft palate is about 2:1 (male:female).[40] In Japanese populations, cleft lip and palate shows a significant male excess, but this excess is not seen for cleft lip alone.[48] In white populations, the male excess in cleft lip with or without cleft palate becomes more apparent with increasing severity of cleft and less apparent when more than one sibling is affected in the family.[49,50] By contrast, the male predominance in cleft lip with or without cleft palate is smaller when the infant has malformations of other systems,[41] and findings of one large study suggest predominance in females when the father is age 40 years or older.[51]

Cleft lip with or without cleft palate and isolated cleft palate are associated frequently with other major congenital anomalies. The proportion of individuals with additional anomalies varies greatly between studies but, in general, further defects seem to be more frequent for people with isolated cleft palate than for those with cleft lip with or without cleft palate.[40] Presence of an anomaly of another system might stimulate a detailed clinical examination, leading to detection of mild cleft palate that otherwise might not have been reported had it arisen in isolation. In a study of almost 4000 individuals with isolated cleft palate in Europe, 55% of cases were isolated, 18% were recorded in association with other anomalies, and 27% were noted as part of recognised syndromes.[52] For cleft lip with or without cleft palate, in a report of more than 5000 patients, 71% of cases were isolated and 29% were seen in association with other anomalies.[53] Adoption of a standardised classification of clefts, such as that suggested by Tolarova and Cervenka,[54] would be helpful.

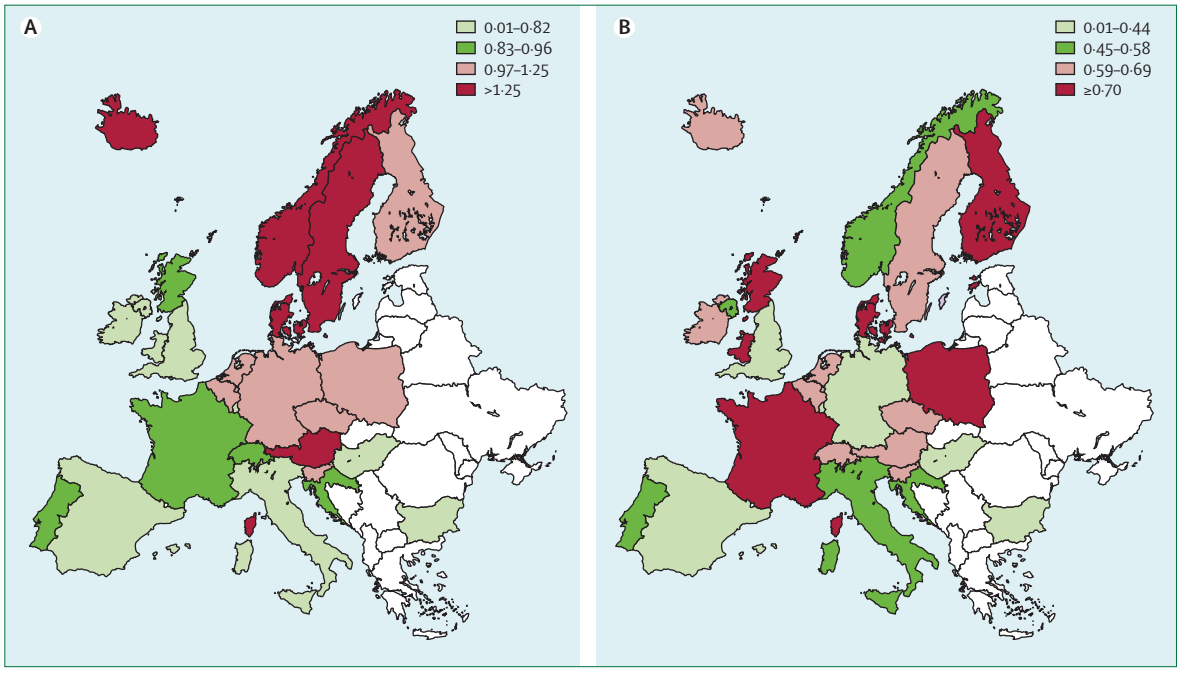

Figure 2: **European birth prevalence per 1000 livebirths of non-syndromic cleft lip and palate**
(A) Cleft lip with or without cleft palate. (B) Isolated cleft palate. Reprinted with permission of the Eurocran project (http://www.eurocran.org).

Consistent associations between orofacial clefts and socioeconomic status have not been established,[55] which could be attributable to differences in measurement and classification of socioeconomic status, differential participation in case-control studies, and variations in inclusion criteria for cases. However, many of the world's most deprived populations do not have surveillance systems for birth defects, and the perception that prevalence at birth is high in some of these regions is not evidence based. The WHO International Collaborative Research on Craniofacial Anomalies project is currently addressing gaps in birth defects surveillance, particularly in developing countries.

Lifestyle and environmental risk factors

Epidemiological and experimental data suggest that environmental risk factors might be important in cleft lip and palate, and maternal exposure to tobacco smoke, alcohol, poor nutrition, viral infection, medicinal drugs, and teratogens in the workplace and at home in early pregnancy have all been investigated. This work is reinforced by the finding that pregnancy planning confers protection.[56,57]

Maternal smoking during pregnancy has been linked consistently with increased risk of both cleft lip with or without cleft palate and isolated cleft palate, with a population-attributable risk as high as 20% (figure 3).[58,59] This association might be underestimated because passive exposure to smoke has not been assessed in most studies. Maternal alcohol use is a well known cause of fetal alcohol syndrome; however, the role of alcohol in isolated orofacial clefts is less certain, with positive associations reported in some studies[60–62] but not others.[63,64] Social and dietary contexts of alcohol consumption are varied and complex and can include modifying or confounding effects of nutrition, smoking, stress,[65] or drug use.

Findings of observational studies suggest a role for maternal nutrition in orofacial clefts, even though assessments of dietary intake or biochemical measures of nutritional status are challenging and generally are not available in many impoverished populations with the highest rates of orofacial clefts. In future studies, measurement of exposure should be enhanced and harmonised across studies, data pooled, and full account made for potential confounding.

In most studies, maternal use of multivitamin supplements in early pregnancy has been linked to decreased risk of orofacial clefts; in a meta-analysis,[66] multivitamin use was associated with a 25% reduction in birth prevalence of orofacial clefts. Data suggest a possible interaction between maternal hyperthermia during pregnancy and use of vitamin supplements, such that supplementation diminishes the increased risk for orofacial clefts associated with hyperthermia.[67] To ascertain from this work which nutrients are protective is difficult, and whether other healthy behaviours of multivitamin users confound these results is unknown.

Previous trials to investigate maternal multivitamin supplementation for prevention of orofacial clefts have been inadequate because of small sample sizes and insufficient data to allow evaluation of results.[68,69] In a Hungarian trial of multivitamins for primary prevention of birth defects the rate of neural-tube defects was significantly lowered, but the study was too small to ascertain whether multivitamins prevented orofacial clefts.[70] The control group received trace elements, including zinc, which could be protective against cleft lip, cleft lip and palate, and cleft palate alone, therefore possibly obscuring a treatment effect. In another randomised controlled trial, in which women choosing to take folic acid supplements before or during pregnancy were randomly allocated either high-dose (2·5 mg) or low-dose (1·0 mg) folic acid,[71] prevalence of orofacial clefts was higher in the high-dose group than in the low-dose group.

Folate deficiency causes clefts in animals,[72] and folate antagonists are associated with increased risk of orofacial clefts in people.[73] The role of dietary or supplemental intake of folic acid in human cleft disorders is uncertain. In North America, where fortification of grains with folic acid has been mandatory since the late 1990s, some evidence suggests a decline in prevalence at birth of cleft lip with or without cleft palate,[74,75] but this outcome has not been recorded in Australia, where fortification was voluntary.[76] For all clefts combined, a decrease was seen in the USA[77] but not in Canada[78] or Chile.[79] Findings of case-control studies of multivitamin supplements containing folic acid,[80–85] maternal dietary folate intake,[81,84,86] and red cell and plasma folate[87–90] are inconsistent.

Raised mean serum concentrations of homocysteine (determined partly by folate status) in mothers of infants with cleft lip, cleft lip and palate, or cleft palate alone have been reported.[87,88] Vitamin B6 (pyridoxine and related compounds) is also a cofactor in homocysteine metabolism and reduces the occurrence of these clefts in animals.[91] Biomarkers of poor vitamin B6 status were associated with increased risk of orofacial clefts in the Netherlands[87] and the Philippines.[89] Vitamin B6 deficiency is typical in populations with high intakes of polished rice in Asia, and these groups also seem to have high rates of cleft lip, cleft lip and palate, and cleft palate alone.[89]

Zinc is important in fetal development, and deficiency of this nutrient causes isolated cleft palate and other malformations in animals.[92] Mothers of children with cleft lip, cleft lip and palate, or cleft palate alone in the Netherlands had lower concentrations of zinc in erythrocytes than did mothers of children without clefts, and similar differences were noted between children with and without these defects.[93] In the Philippines, zinc deficiency is widespread, and high maternal amounts of zinc in plasma were associated with low risk of orofacial clefts with a dose-response relation.[94]

For the **WHO International Collaborative Research on Craniofacial Anomalies project** see http://www.who.int/genomics/anomalies/cfaproject

Other nutrients that could play a part in development of orofacial clefts include riboflavin[95] and vitamin A.[96,97] Fetal exposure to retinoid drugs can result in severe craniofacial anomalies,[98] but the relevance of this finding to dietary exposure to vitamin A is uncertain.

Maternal occupational exposure to organic solvents[99] and parental exposure to agricultural chemicals[100,101] have been associated inconsistently with cleft lip, cleft lip and palate, and cleft palate alone. Anticonvulsant drugs, notably diazepam, phenytoin, and phenobarbital,[102–104] increase risk of these anomalies. Positive associations with maternal corticosteroid use in pregnancy have been reported.[105] Such findings must be interpreted cautiously because of possible publication bias.

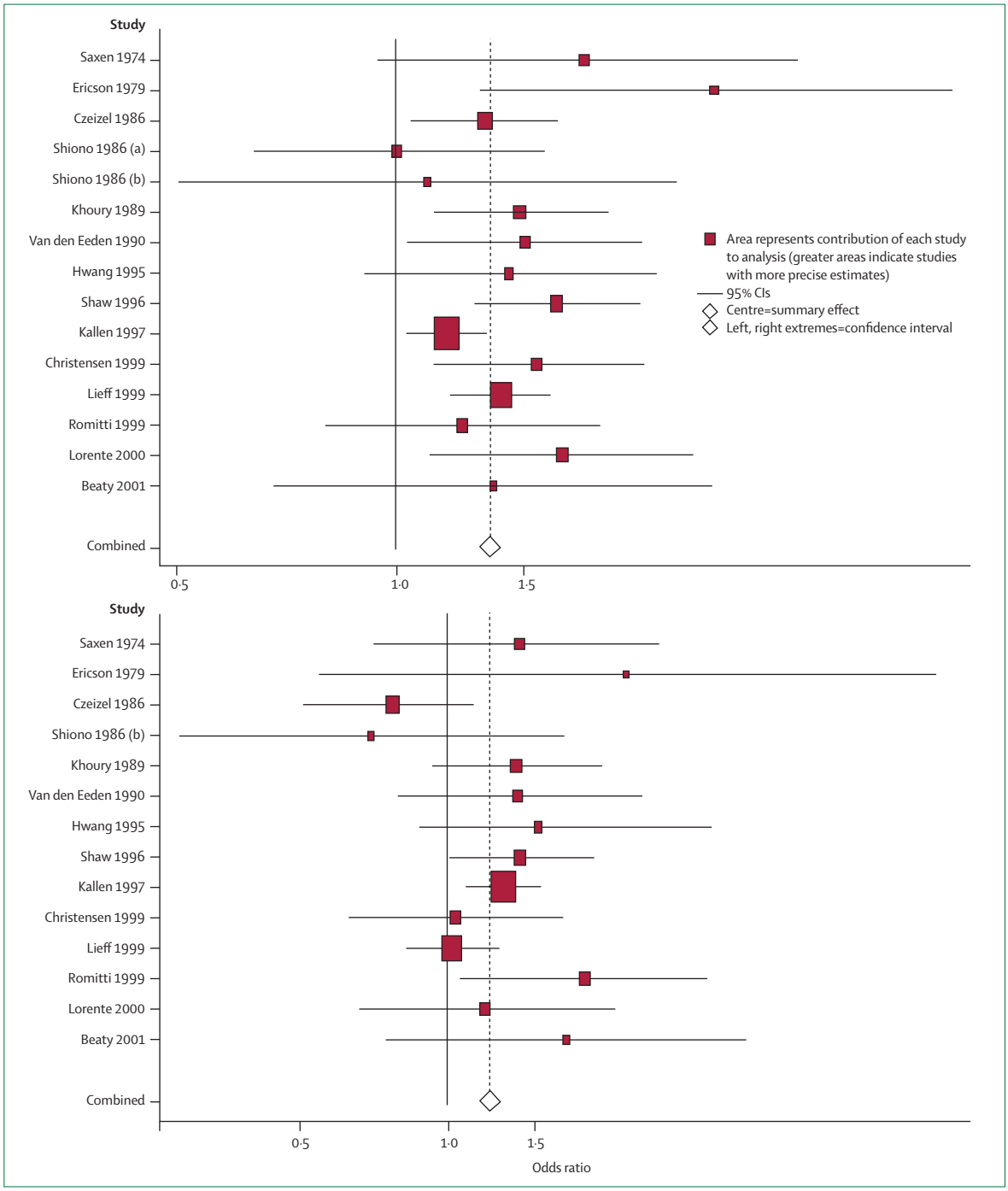

Figure 3: **Forest plots of maternal smoking and cleft lip with or without cleft palate (upper) and isolated cleft palate (lower)**
Reprinted from reference 58, with permission of the World Health Organization.

Interferon regulatory transcription factors are activated after viral infection. Association of *IRF6* with clefts raises the possibility that viral infection in the first trimester of pregnancy might enhance risk of a cleft.[106]

Genetic factors

Cleft lip with or without cleft palate is listed as a feature of more than 200 specific genetic syndromes, and isolated cleft palate is recorded as a component of more than 400 such disorders.[107] The proportion of orofacial clefts associated with specific syndromes is between 5% and 7%.[108] If specific genetic disorders are excluded, the recurrence risk to siblings is greater than that predicted by familial aggregation of environmental risk factors.[109] Concordance rates for cleft lip, cleft lip and palate, and cleft palate alone are higher in monozygotic twin pairs than in dizygotic pairs.[110] The familial clustering and concordance recorded in twins with cleft lip with or without cleft palate and isolated cleft palate is specific for each defect, and therefore the anomalies are thought to have heterogeneous causes.[111–113] Predominance of left-sided clefting and the male excess of cleft lip with or without cleft palate[40] also suggest the importance of genetic susceptibility. Findings of segregation analyses indicate that the number of genes implicated is likely to be fairly small: three or four major loci were reported in an analysis of data from the west of Scotland,[114] and two to 14 loci were recorded by analysis of familial datasets from England.[115] The patterns might differ according to ascertainment, environmental contribution, and population gene-pool effect.[116,117]

Findings of linkage studies have suggested various loci could have a causal role in cleft lip and palate,[118,119] including regions on chromosomes 1, 2, 4, 6, 14, 17, and 19 (*MTHFR*, *TGFA*, D4S175, *F13A1*, *TGFB3*, D17S250, and *APOC2*), with putative loci suggested at 2q32–q35 and 9q21–q33. Inconsistency of results could indicate the small size of studies or genetic heterogeneity.

Various genetic polymorphisms have been investigated in population-based association studies. Some gene products studied are growth factors (eg, TGFA, TGFβ3), transcription factors (eg, MSX1, IRF6, TBX22), or factors that play a part in xenobiotic metabolism (eg, CYP1A1, GSTM1 [glutathione S-transferase μ1], NAT2 [N-acetyltransferase 2]), nutrient metabolism (eg, MTHFR [methylenetetrahydrofolate reductase], RARA [retinoic acid receptor α]), or immune response (eg, PVRL1, IRF6). The most intensively investigated variants have been of the *TGFA*[120–122] and *MTHFR*[66,123,124] genes. Data have been inconsistent, indicating the challenges of researching gene-disease associations and related interactions.[125]

The gene *IRF6*, which has a causal association with van der Woude's syndrome, is also linked strongly to the isolated form of clefting.[126] This finding has been replicated in many different populations and ethnic groups (figure 4).[127–130] Variants of genes linked to syndromic forms of cleft lip with or without cleft palate that have a mendelian mode of inheritance can also produce phenocopies of non-syndromic clefts.[5] This observation suggests that a strategy of choosing variants of genes associated with syndromic forms of cleft lip with or without cleft palate as candidates for investigations into the cause of non-syndromic clefts could be productive. Other examples of mendelian-inherited syndromes and related genes that, if mutated, could result in or modify the expression of cleft lip with or without cleft palate include Kallmann's syndrome (*FGFR1*),[131] ectrodactyly, ectodermal dysplasia, and clefting syndrome (*TP63*),[132,133] X-linked clefting and ankyloglossia (*TBX22*),[134] Gorlin's syndrome (*PTCH1*),[135] and Margarita Island ectodermal dysplasia (*PVRL1* [heterozygous]).[136]

Although discovery of the genetic cause of van der Woude's or popliteal pterygium syndromes will have no immediate therapeutic benefit, advantages for diagnosis are instant, and this knowledge will be potentially useful in genetic counselling. If one gene mutation, which can be identified by prenatal diagnosis, causes cleft lip, cleft lip and palate, or cleft palate alone in a proportion of people, identification of individuals at high risk of having children with the same defect will be possible.

Fitzpatrick and colleagues[137] have studied rare, apparently balanced, chromosomal rearrangements associated with isolated cleft palate and have identified *SATB2* as an important gene in development of the human secondary palate. This group of researchers has identified several other chromosomal aberrations that strongly suggest misregulation of *SOX9* in Pierre Robin sequence. Jakobsen and co-workers[138] reported that the genes *PVRL1* (chromosome 11) and *GAD1* (chromosome 2) might also contribute to the cause of Pierre-Robin sequence. Genome-wide association is emerging as a powerful technique in polygenic diseases, and is expected to play a part in discovery of the genetic cause of orofacial clefts in the future.[139]

Gene-environment interaction

Investigation of gene-environment interaction is important for several reasons. First, estimates of the main effects of genes or environment could be biased if interaction is not taken into account.[140] Second, our understanding of cause and pathogenesis is enhanced by such studies. Finally, findings of interaction work can inform decisions about public health strategies.

With respect to cleft lip and palate, many potential interactions have been tested. Genes and risk factors investigated in such studies include: *TGFA* and smoking[141–143] and vitamin supplements;[144] *TGFB3* and smoking and alcohol;[60,145,146] *MSX1* and smoking and alcohol;[60,146,147] polymorphisms affecting xenobiotic metabolism (eg, *EPHX1* [epoxy hydrolase], *GSTM1*, *GSTT1*, *NAT1*, *NAT2*, or *CYP1A1*) and smoking,[148–150] occupational exposures,[98] and maternal medicinal drug use;[151] *RARA*

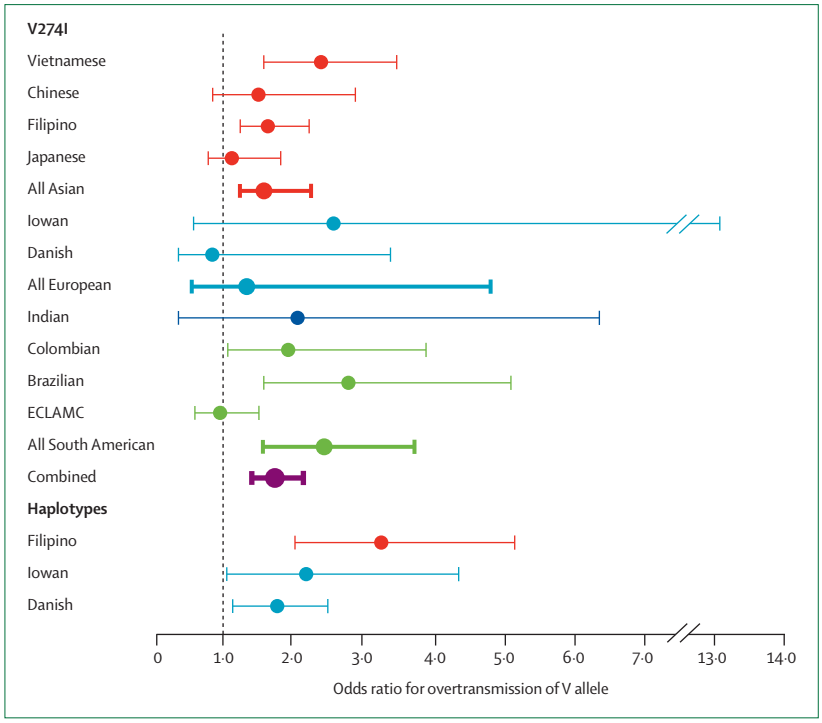

Figure 4: **Overtransmission of polymorphisms at *IRF6* locus**
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polymorphisms and maternal intake of vitamin A;[96] and polymorphisms affecting folate metabolism (eg, *MTHFR*, *RFC1*) and maternal folate intake.[60,88,90,152–154]

Findings on interactions have been inconclusive. Reasons for uncertainty include: low statistical power to detect or exclude interaction; differences between studies in the individuals who have been genotyped (eg, mother alone or with infant); research confined to populations in a few industrialised countries; and non-existent or unreported replication work. Establishment of a collaborative group has been proposed, through the WHO International Collaborative Research on Craniofacial Anomalies project, to undertake meta-analyses and pooled analyses of studies of relations between craniofacial anomalies and putative genetic polymorphisms. Furthermore, gene variants are usually considered one at a time, whereas, a priori, variants of many genes might be expected to modulate the effects of an exposure.[155]

For the **Eurocran project** see http://www.eurocran.org

Clinical management

Services and treatment protocols for management of children with cleft lip and palate can differ remarkably within and between developed countries. In Europe, a networking initiative funded by the European Union in the late 1990s reached consensus on a set of recommendations for cleft care delivery, which were subsequently adopted by WHO.[5] However, findings of a network survey indicated that these guidelines were seldom matched in practice.[156]

The absence of a sound evidence base for selection of treatment protocols was shown by a striking diversity of practices across Europe for surgical care of just one cleft subtype—unilateral complete cleft of lip, alveolus, and palate. Of 201 teams doing primary surgical repair for this defect type, 194 different protocols were being practised. Even though 86 (43%) groups closed the lip at the first operation and the hard and soft palate together at the second, 17 possible sequences of operation to close the cleft were being used. One operation was needed to completely close the cleft in ten protocols (5%), two were needed in 144 (71%), three operations were used in 43 (22%), and four were needed in four protocols (2%). Around half used presurgical orthopaedic techniques with mostly passive plates and some teams also used a plate to assist with feeding.

These uncertainties in treatment indicate the paucity of published randomised trials of cleft care.[5] Such studies present particular challenges for planning and recruitment in comparison of surgical techniques, because trial protocols must take account of the surgical learning curve. However, several well-planned, large-scale, surgical randomised controlled trials are now in follow-up periods (figure 5). So far, only a brief systematic review of cleft care has been published,[157] as has a systematic review of prevalence of dental caries in children with clefts.[158]

Reliability of prenatal ultrasonographic diagnosis has been increasing, although sensitivity is still low, particularly for cleft palate.[159,160] The rate of termination of pregnancy because of presence of a cleft varies between countries, but it remains generally low.[161] Genetic testing in the future could enhance sensitivity and specificity of prenatal diagnosis for syndromic and non-syndromic orofacial clefts.

Service organisation, inequality of care, and treatment uncertainty are widespread issues,[5,41] and scarce resources put basic surgical treatment beyond the reach of thousands of children in developing countries. Accordingly, WHO have highlighted the need for effective international collaboration on strategies to enhance clinical care, through interaction of regional cooperatives such as the Eurocran project. Several research priorities were noted by WHO, including: surgical repair of different orofacial cleft subtypes; surgical methods for correction of velopharyngeal insufficiency; methods for management of perioperative pain, swelling, and infection; and nursing. Clinical trials of these issues would need to include sufficient numbers of patients to be of adequate power. Other multidisciplinary studies of cleft care might include: use of prophylactic ventilation tubes (grommets) for middle-ear disease; presurgical orthopaedic techniques; methods to achieve optimum feeding before and after surgery; and different approaches to speech therapy. In developing countries, trials need to address affordable surgical, anaesthetic, and nursing care.

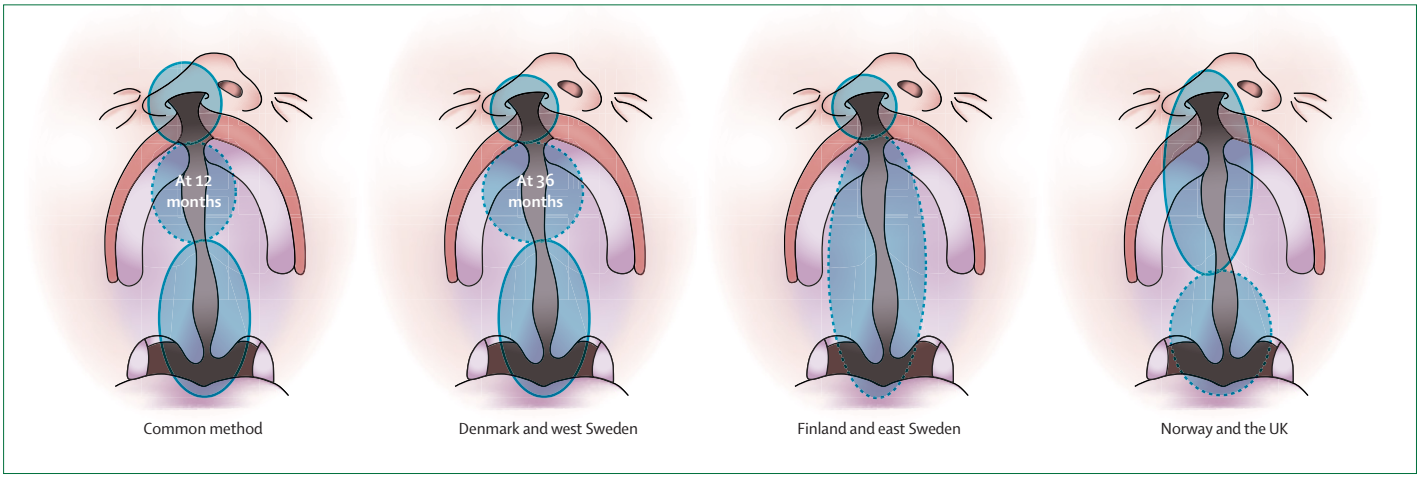

Figure 5: **Techniques used for surgical repair of complete unilateral cleft lip and palate**
Dotted and full circles indicate parts of the cleft that are repaired at different times in various randomised surgical protocols. When there are two full circles, these repairs were completed during the same surgical procedure. Reprinted with permission of the Eurocran project (http://www.eurocran.org).

International adoption of guidelines for provision of clinical services and for maintenance and analysis of minimum clinical records of cleft care is desirable to hasten cohort studies across centres. Various registries of clinical outcomes have emerged and are working independently. Efforts should be made to harmonise these initiatives.

For rare interventions, prospective registries should be established to accelerate collaborative monitoring and critical appraisal, equivalent to phase I trials. Relevant topics would be craniosynostosis surgery, ear reconstruction, distraction osteogenesis for hemifacial macrosomia and other skeletal variations, midface surgery in craniofacial dysostosis, and correction of hypertelorism.

Another urgent issue is the need to create collaborative groups (or to enhance networking of existing groups) to develop and standardise outcome measures. Work on psychological and quality-of-life measures and economic outcomes is needed especially urgently. Collaboration between clinicians and laboratory-based scientists is also essential, not only to describe phenotype much more sensitively than has been done hitherto but also to augment knowledge translation from bench to bedside. Such collaboration has not yet happened in the description and ascertainment of the importance of microforms. Findings of many orofacial clefting studies in various populations have shown that parental craniofacial phenotype is distinctive when compared with that of the non-cleft population.[162] Additional so-called microforms in orbicularis oris morphology and activity,[163] dermatoglyphics,[164] non-right-handedness,[165] anomalies of the cervical spine,[166] and tooth dysmorphology[167] have also been reported. Genotype-phenotype correlation research in this area could yield important information on risk factors.

In large parts of the world, routine public health services cannot afford treatment for cleft lip and palate. Other solutions, incorporating various amounts of charitable and non-governmental support, include high-volume indigenous centres of excellence, contracts between non-governmental organisations and local hospitals, and volunteer short-term surgical missions. WHO recommends promotion of dialogue between different non-governmental organisations to develop agreed codes of practice and adopt the most appropriate forms of aid for local circumstances, with emphasis on support that favours indigenous long-term solutions.

Primary prevention of orofacial clefts

Identification of modifiable risk factors for oral clefts is the first step towards primary prevention. Such preventive efforts might entail manipulation of maternal lifestyle, improved diet, use of multivitamin and mineral supplements, avoidance of certain drugs and medicines, and general awareness of social, occupational, and residential risk factors. The proportion of clefts attributable to maternal smoking in populations with a high prevalence of smoking in women of reproductive age was estimated at 22%.[168] However, the link with smoking was not even mentioned in international reports on smoking and health.[5,169,170] Tobacco use is rapidly increasing in women of reproductive age in many countries because they are targeted actively by tobacco marketing campaigns.[169,171] Pictures of children's faces have been used to establish some of the world's largest medical charity organisations devoted to surgical repair of orofacial clefts. A similar approach might prove effective in public health campaigns to reduce tobacco use by women.[5]

Multivitamin and mineral supplements are associated consistently with reduced risk of cleft lip, cleft lip and palate, and cleft palate alone. However, adverse effects of long-term use of supplements containing antioxidant vitamins have been reported;[172] therefore, clarification of

the specific nutrients and minerals that account for this apparent inverse association is important.

Clinical trials will ultimately be needed to test nutritional hypotheses for prevention of orofacial clefts. A US-Brazilian collaborative randomised controlled trial has been implemented to address whether high-dose folic acid supplementation is more effective than a lower dose to prevent recurrence of non-syndromic cleft lip with or without cleft palate. To be definitive, however, trials will need to be large and—for reasons of efficiency and public health effect—a range of reproductive outcomes should be examined simultaneously. The next reasonable step for research into orofacial clefts might be observational studies of nutrients and food groups, genes, and metabolism to narrow the range of candidate nutrients.

Conclusions

Large, multicentre, collaborative studies[125] are needed to elucidate both environmental (including lifestyle) and genetic risk factors for cleft lip and palate and interactions between them. Exposure measurement is challenging; cleft lip, cleft lip and palate, or cleft palate alone should be encouraged as an endpoint in cohort studies of reproductive outcome, and exposure assessment needs to be harmonised in such studies. The Public Population Project in Genomics is an international consortium to promote collaboration between researchers in population genomics and is an initiative that would help to harmonise data from large-scale, prospective, cohort studies, helping to enhance comparability of studies feeding in to pooled analyses of gene-environment interaction. Similarly, collaborations are needed to elucidate better the issues surrounding management of orofacial clefts, to establish equipoise between different options, to undertake randomised controlled trials and other evaluations of interventions, and to facilitate knowledge translation.

For the **Public Population Project in Genomics** see http://p3gconsortium.org/

Conflicts of interest

We declare that we have no conflicts of interest.

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SCIENTIFIC REVIEW

Congenital Anomalies in Low- and Middle-Income Countries: The Unborn Child of Global Surgery

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Abstract Surgically correctable congenital anomalies cause a substantial burden of global morbidity and mortality. These anomalies disproportionately affect children in low- and middle-income countries (LMICs) due to sociocultural, economic, and structural factors that limit the accessibility and quality of pediatric surgery. While data from LMICs are sparse, available evidence suggests that the true human and financial cost of congenital anomalies is grossly underestimated and that pediatric surgery is a cost-effective intervention with the potential to avert significant premature mortality and lifelong disability.

Introduction

If surgery is the "neglected stepchild of global health" [1], pediatric surgery is the child not yet born. Despite powerful strides forward in the treatment of congenital anomalies, or birth defects, the benefits of these diagnostic and therapeutic advances have been largely confined to high-income countries (HICs), where many once fatal conditions can now be treated, with mortality rates under 10 %. In contrast, mortality rates from hospital-based data in low- and middle-income countries (LMICs) for common anomalies often rise to 20–85 % [2–17]. Patients with immediately life-threatening conditions may die in transit or at home, and never be entered into such hospital-based measures [18, 19]; the resultant hidden mortality represents an oft-underestimated addition to the burden of disease. This review article will summarize the growing body of knowledge on surgical congenital anomalies in LMICs and will highlight key research recommendations. An expanded version of this review will be published as a book chapter in *Disease Control Priorities 3, Volume 3: Essential Surgery*.

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Congenital anomalies and the global burden of disease

Congenital anomalies account for a staggering 25.3–38.8 million disability-adjusted life-years (DALYs) worldwide [20, 21]. DALYs are a well established metric for measuring the burden of disease in terms of both mortality and morbidity; 1 DALY is 1 healthy year of life lost due to

disability or premature death. The World Health Organization's (WHO) recent global burden of disease (GBD) study reports that anomalies rank 17th in causes of disease burden [20]. While impressive, these figures are likely underestimates due to the limited number of anomalies included and the difficulties in evaluating incidence, morbidity, and mortality. Only six anomalies were assigned disability weights in the previous 2004 estimates, and new disability weights were not estimated for congenital anomalies in 2012 [21, 22]. Some researchers have tried to fill the gap with evidence-based estimates of selected disability-weights [23]. Of the conditions measured in the GBD study, cardiac defects represent the greatest overall burden, and, with neural tube defects and cleft lip and palate, cause 21 million DALYs. Of these, 57 %, or 12 million are estimated to be surgically avertable if outcomes in HICs could be achieved in LMICs [24]. The GBD study also reports 361 DALYs per 1,000 population globally [20]. Strikingly, congenital anomalies may be responsible for up to 120 DALYs per 1,000 children [25].

In general, current estimates of the surgical burden of disease are considered a "best educated guess," given the "near total lack of pertinent data" [26]. Even less is known about pediatric surgical disease [27]. Extant research paints a brutal picture of the potential scope and human cost of pediatric surgical disease.

Incidence, prevalence and treatment of congenital anomalies in LMICs

A total of 94 % of anomalies occur in LMICs [28]. Higher fertility rates translate to higher birth rates and net prevalence of anomalies. In addition, the frequency of pregnancy termination following prenatal diagnosis of a congenital anomaly is lower in many LMICs than in HICs. In part, this difference stems from the fact that elective pregnancy termination following prenatal diagnosis may be less available in certain LMICs than in HICs. Despite a global trend towards liberalization of termination laws, legal and procedural pushback limit access to pregnancy termination services in many countries around the world [29].

Incidence (the frequency with which a disease occurs in a given population) is also higher in LMICs. This jump has been attributed to an interaction of multiple contextual factors, including increased nutritional deficiency, prevalence of intrauterine infection, exposure to teratogens, and self-medication with unsupervised drugs or traditional remedies [30, 31]. Although decreasing the birth rate may reduce the net prevalence of congenital anomalies, most anomalies cannot otherwise be prevented and must be treated surgically.

Many LMICs lack rigorous congenital anomaly surveillance programs, making accurate calculations of incidence and prevalence difficult [31]. Current calculations, which range from 4 to 12 cases per 1,000 births, are likely underestimates due to stigma and exclusion [32–34]. In addition, the emergent nature of some anomalies can skew incidence and prevalence data. Children with non-immediately life-threatening anomalies are more likely to survive until treatment than children with immediately life-threatening conditions. Hospital-based data therefore inherently biases the perception of relative incidence and prevalence such that immediately life-threatening conditions may appear to have a lower incidence than non-immediately life-threatening anomalies [35]. Population-based surveys—which directly collect data from non-centralized sites—represent one approach to addressing this challenge [25].

The burden of disease associated with congenital anomalies in LMICs is most often calculated as the mortality rate over a given period of time. These data can be challenging to analyze in LMICs. In Benin, for example, only 0.8 % of nearly 1,100 neonatal deaths were investigated with an autopsy. In all examined cases, autopsy provided additional information on the cause of death [36]. Additionally, non-fatal anomalies can result in extensive, ongoing morbidity. The burden of disease is grossly underestimated if measures of this impairment are not included. Indeed, anomalies resulting in visible deformity (such as clubfoot and cleft lip) or non-visible anomalies that cause chronic disability may also cause stigmatization, which can trigger abandonment or infanticide. An 'incurable' anomaly may endanger the whole family's well-being, as key resources must be allocated to care for the afflicted child. Families may fracture, with one or both parents leaving the child with other family members. While extant calculations of the burden of disease neglect to measure these harms, these calculations do highlight marked disparities in survival rates between HICs and LMICs.

Heightened mortality rates stem from a complex web of social, economic, and geographic factors. In LMICs, many births occur at home, either with no attendants or with traditional birth attendants; pejorative cultural beliefs or ignorance about possible cures for defects may prevent families from seeking treatment. If families do seek care, they must often travel great distances to reach medical facilities. Hypothermia is common following unsupervised transport over long distances, with severe repercussions on outcomes [13, 14, 37]. Misdiagnosis as better known infectious diseases is common, as are added delays in diagnosis for non-visible anomalies. These challenges are exacerbated by the paucity of specialized providers in LMICs. One pediatric general surgeon may serve millions

of children [38], and physicians performing pediatric surgery may have little or no pediatric surgery training [39, 40]. While North America has an estimated one pediatric cardiac surgeon per 3 million people, sub-Saharan Africa has one per 38 million people [41]; 75 % of the world's population is estimated to have no access to cardiac surgery [42]. Similarly, one-third of the world's population is covered by one-twentieth of its neurosurgeons [43]. Delays in referring patients from local health centers to medical centers with specialized surgical capacity, and the financial burden of treatment on families, also limit the accessibility of treatment for congenital anomalies.

The power of pediatric surgery to reduce the global burden of disease

Only a small body of literature evaluates the potential of surgery to reduce the burden of disease associated with congenital anomalies in terms of DALYs averted or cost effectiveness. Yet these foundational studies have provided compelling evidence that pediatric surgery represents a cost-effective intervention with the potential to avert over two-thirds of the DALYs associated with birth defects [24, 25, 34, 44–46]. Favorable outcomes have been reported in HICs for anomalies such as anorectal malformations and congenital diaphragmatic hernia [47]. In LMICs, the human capital approach to cleft lip and palate repair has provided very favorable cost-effectiveness analysis (CEA) estimates. An extension of this methodology to treatment for hydrocephalus in Uganda yielded a cost of $US59–126 per DALY averted [48]. Surgical repair of congenital inguinal hernias in Uganda was estimated to have an incremental cost-effectiveness ratio (ICER) of $US12/DALY averted [49]. Another recent report from Cambodia estimated a CEA of $US99/DALY averted over 3 months for reconstructive surgery for an array of anomalies [50].

Critically, treating congenital anomalies may translate into a significantly greater reduction in the economic burden of disease than that cited above. Since children represent the future economic engine powering LMICs, the value of investing in pediatric surgery also encompasses the future socioeconomic well-being of LMICs. In order to take advantage of the inherent upside to treating congenital disease at its inception, research must address the knowledge gaps that currently impede the development of effective care systems.

Recommended research priorities for pediatric surgery in LMICs

Based on the available literature, research priorities to improve pediatric surgery capacity and reduce the burden of disease attributable to congenital anomalies include the following:

1. Epidemiology, prevalence, and incidence of disease. Epidemiology may vary locally, but additional data are needed [51]. Registries for selected anomalies may assist in improving surveillance (e.g. by participation in the International Clearinghouse for Birth Defects Surveillance and Research). Evaluation of hidden mortality and morbidity will better approximate the true burden of disease.
2. Pediatric surgical capacity at all levels of the health system. Guidelines for minimum human resources and infrastructure for countries at different levels of development. While the WHO Situational Analysis Tool (which evaluates gaps in the availability of emergency and essential surgical care) only includes two items pertaining to pediatric surgical care, an alternative capacity tool has recently been proposed [52]. This tool could be refined and further evaluated as it is piloted in different countries. While surgical outreach programs tackle the backlog of non-emergent conditions, emergent conditions require development of the whole health system. More work is needed to define and develop the mechanisms to strengthen systems for pediatric surgery.
3. Optimized quantitative metrics of disease burden. While well accepted, DALYs are difficult to apply practically. Surgical backlogs can be calculated for congenital anomalies and can be a useful advocacy tool to estimate the resources needed to treat common, non-fatal anomalies. In MICs and HICs, many prevalent congenital anomalies are treated in the first year of life; in LICs, they are never treated or are treated years later, after children have suffered unnecessary complications. Improved measurements of the burden imposed by delayed access to care have not yet been developed. However, as DALYs are currently the standard metric, calculating new or better disability-weights for a broad range of congenital anomalies is also a viable means by which to improve meaningful evaluation of the contribution of congenital anomalies to the global burden of disease.
4. Models for the integration of pediatric surgical services within existing child health initiatives. Large-scale child health initiatives (such as the WHO Integrated Management of Childhood Illness and Neonatal Resuscitation) have not historically included surgical care. Similarly, congenital anomalies have not been addressed through the agenda of the non-communicable disease movement, despite the fact that they are at times considered non-communicable disease (as in the WHO's recent GBD study). Many

providers of children's surgical services share the concern that the surgical needs of children, if not explicitly addressed, are often neglected. Additionally, greater planning is needed between networks of specialty organizations and providers treating a broad range of congenital anomalies to collaborate where possible.

5. Cost-effectiveness data. To the author's knowledge, only two attempts to estimate cost effectiveness for pediatric surgical wards has been made [34, 50]. Low-cost technical and technological innovations (such as telemedicine) hold great promise to improve perioperative care and training [53]. CEA of training programs could also aid in advocacy for greater resources for training.
6. Aligning marketing and advocacy. Greater emphasis has been directed toward selected visible, treatable anomalies (e.g. cleft lip and palate) than to a range of anomalies for which it has been more difficult to engage donor programs. Innovative strategies to improve the multidimensional measurement of the burden of disease are needed to make these treatable anomalies more salient for the public health community.

Conclusion

Great disparities exist in the accessibility and quality of pediatric surgical services between HICs and LMICs. This gap can only be bridged by jointly building pediatric surgical capacity in LMICs and by conducting rigorous research to better guide health system development and allocation of inherently limited resources. Local expertise and buy-in should be integrated whenever possible in order to create sustainable systems that increase long-term capacity and take advantage of the substantial potential intellectual, creative, and personnel resources of LMICs. It is an economic and moral imperative that global partners invest in pediatric surgery as a vital component of reducing the burden of disease and improving the public health and economic fortunes of LMICs. Healthy children remain the only future for society.

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Congenital anomalies in the context of global surgery

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ABSTRACT

Surgery is increasingly recognized as an essential component of global health development. This article will review the state of global pediatric surgery, utilizing congenital anomalies as a framework in which to discuss the promise of pediatric surgery in reducing the global burden of disease. Congenital anomalies are responsible for a substantial burden of morbidity and mortality in low- and middle-income countries (LMICs), as well as significant emotional and economic harms to the families of children with congenital anomalies. Limited pediatric surgical capacity in many LMICs has culminated in a devastating burden of avertable disability and death. Pediatric surgery is an effective and cost-effective means to reduce this burden. Pediatric surgeons must continue to drive the growth of global pediatric surgery by engaging in clinical practice, educational partnerships, and research initiatives.

Introduction

Surgical disease is responsible for an estimated 11–30% of the global burden of disease.[1] In the 2010 World Health Organization (WHO) Global Burden of Disease Study,[2] which described the worldwide distribution of morbidity and mortality, surgery was essential to the diagnosis and treatment of patients in all of the disease categories described (injury; non-communicable diseases; communicable, maternal, neonatal, and nutritional diseases), underscoring surgery's role as a pillar of healthcare in both low- and middle-income countries (LMICs) and high-income countries (HICs).[3–5] Overall, 321.5 million more inpatient surgical procedures are needed to meet the global need; the surgical need in terms of top disease indication varies between regions and countries, further underscoring the importance of surgery across healthcare systems, regardless of individual regional or national health priorities.[3]

Historically, surgery was considered "too costly and too complex" for inclusion in health development projects in LMICs, "a luxury to be afforded only by the wealthy elite."[6] This misconception, in combination with vertical approaches to public health which focused on particular diseases, largely rendered surgery a *persona non grata* in the world of health development[6,7] However, as mounting research reinforces that surgery is and should be considered as an integral component of improving global health and well-being, global health stakeholders and leaders have increasingly recognized the importance of surgery in reducing the global burden of disease, and have initiated projects to support the growth of global surgery.[7]

Much work remains to be done before global surgery can live up to its promise. 67% of the world's population, or approximately 4.8 billion people, do not have access to surgical care, when access is defined by availability, timeliness, safety, and affordability.[8] In some regions of the world, such as sub-Saharan Africa and Southeast Asia, over 95% of the population does not have access to surgical care.[8] Among the LMICs for which national surgical workforce data is available, the density of general surgeons ranges from 0.13 to 1.57 per 100,000 population, and the density of anesthesiologists from 0 to 4.9 per 100,000 population.[9] Foreign investment in the development of surgical systems is also limited. The Institute for Health Metrics and Evaluation's Development Assistance for Health Databases suggests that the total assistance targeted to surgical initiatives in LMICs by HICs is relatively minor, representing $< 1\%$ of the total developmental aid the United States *alone* provides to LMICs.[10]

These and other challenges to global surgery as a whole also plague the emerging sub-field of global pediatric surgery. Where global surgery may once have been the "neglected stepchild" of global health, global pediatric surgery was the "child not yet born,"[11] an area of practice about which even less was known.[12] A vanguard of dedicated pediatric surgeons have propelled the

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rapid growth of this burgeoning field, forming international partnerships and spearheading foundational clinical and research initiatives across the world.[13] This review article will provide an updated overview of the state of global pediatric surgery, specifically focusing on surgical care for congenital anomalies as a framework in which to discuss the promise of pediatric surgery in reducing the global burden of disease.

A heavy burden to bear: Congenital anomalies in low- and middle-income countries

Congenital anomalies are increasingly recognized as an important global cause of pediatric disease. The human and financial cost of congenital anomalies is particularly acute in LMICs, in which more than 90% of congenital anomalies are estimated to occur.[14] The incidence of congenital anomalies has been estimated at as much as 12 per 1000 live births.[15] However, as we have reported previously, this and other approximations of congenital anomaly incidence and prevalence in LMICs are likely underestimates due to the absence of national congenital anomaly surveillance systems in many LMICs,[16–18] cultural stigma associated with congenital anomalies, which may impede presentation to healthcare services or even lead to infanticide,[19,20] and the inherent bias of hospital-based data, which by its nature excludes from estimations of incidence and prevalence those infants with immediately life-threatening conditions who die prior to reaching treatment.[21,22]

Much of the data from LMICs describes the regional or national burden of congenital disease in terms of mortality. Such data underscores the vast differences in mortality rates between LMICs and high-income countries (HICs).[18,23] For example, the 30-day mortality rate for infants born with gastroschisis in HICs is 1%[24]; in LMICs, reported mortality rates range from 14% to 100%.[24–33] Similarly, in HICs, mortality rates for infants with congenital heart disease range from 3% to 7%[34]; in LMICs, mortality rates range from 8.8% to 23.5%.[16,35–38] Such disparities in outcomes arise from a network of factors limiting the availability of timely high quality pediatric surgical services. Many births do not occur in a hospital setting, and families must often travel long distances before reaching care, which can result in additional medical complications.[26,30,33] Some families may choose to not seek medical care due to the heavy stigma associated with congenital anomalies, as noted above. Even when families present to care centers, they may be unable to access essential pediatric surgical services due to the dire pediatric workforce shortage in many LMICs[39,40] and the practice limitations that may be imposed by a resource-limited environment, such as decreased availability of life support interventions during and following surgical intervention.[25,26]

The avertable, long-term burden of disease imposed by treatment delays also poses significant threat to the well-being and security of a child's entire family. Unexpected health crises have been reported to cause high rates of "catastrophic spending" in many LMICS, in which out of pocket healthcare expenses push families into poverty.[41] Families at the lower end of economic ladder are particularly vulnerable to catastrophic spending, as out of pocket medical expenses comprise a larger proportion of familial income.[41] Non-communicable disease in the household has also been related to reduced labor force participation among household members and reduced family income, compounding the economic harms to families caring for children with congenital anomalies.[41]

In addition to the costs associated with congenital anomalies described above, data suggests that congenital anomalies contribute significantly to the disease burden in LMICs as described in Disability Adjusted Life Years, or DALYs. DALYs are an established metric for disease burden; each DALY is equivalent to one year of healthy life lost to premature death or to disability. A recent population-based study in Kenya found that eight prevalent anomalies cause 54–126 DALYs per 1000 children.[42] Only 3.5% of neonatal surgical need is met in Uganda, resulting in 145, 225 avertable DALYs lost annually due to the six most prevalent anomalies.[25] This avertable burden is of comparable magnitude to the DALYs lost per 100,000 population attributable to more traditional targets of health development, such as neglected tropical disease.[25] Powerfully, the WHO Global Burden of Disease study identified congenital anomalies as one of the top 20 causes of global morbidity and mortality, accounting for up to 38.8 million DALYs lost annually.[2] Even this sizable burden may in fact be a gross underestimate of the true disease burden imposed by congenital anomalies, as the impacts of only *six* congenital anomalies were included in this analysis.[43]

Coming into its own: Pediatric surgery as an emerging solution to a global problem

A corpus of pioneering work has provided convincing evidence that surgery is both an effective and cost-effective means of dramatically reducing the burden of congenital disease.[44–50] For example, a recent report from Uganda showed that congenital hydrocephalus can be surgically managed for USD $59–$126 per DALY averted.[50] Similarly, congenital inguinal hernias can be surgically repaired with an estimated incremental cost-effectiveness of USD $12 per DALY averted.[51] These measures of cost-effectiveness favorably compare to more traditional global public health initiatives, such as the provision of anti-retroviral drugs in sub-Saharan Africa (USD $350–$1494 per DALY averted).[52]

While these individual case studies illustrate that pediatric surgery for select congenital conditions is cost-effective, preliminary evidence also suggests that pediatric surgical wards overall are also an effective and cost-effective means to reducing the substantial burden of congenital disease. A single surgical pediatric surgical ward in Kenya was reported to annually spare 23,169 DALYs, representing on average 22 DALYs spared per surgical procedure.[47] Pediatric surgical services for congenital and acquired disease cost USD $44–$88 USD per DALY spared in a Kenyan refugee camp.[49] In Cambodia, a pediatric reconstructive surgical ward reported a cost-effectiveness of USD $99 per DALY averted,[53] which, as noted above, compares favorably with other global health interventions.

In line with these pioneering analyses, the true effectiveness and cost-effectiveness of global pediatric surgery must not merely be measured on the level of specific surgeries performed or select congenital conditions treated, but on the systems levels—in other words, the net effect of enhanced and expanded accessibility of high quality pediatric surgical care *across* disease indications and procedures performed. Additional research in this area is desperately needed to support advocacy for increasing pediatric surgical capacity in LMIC and to inform resource allocation by the global health community.

The next step: Opportunities in global pediatric surgery—for pediatric surgeons

Pediatric surgeons are perfectly positioned to help address the pediatric surgery crisis in LMICs in a variety of ways. In LMICs in which one general pediatric surgeon may be clinically active in the entire country,[25,54] the immediate provision of surgical care is an important priority. Surgical missions, also known as surgical volunteer trips, represent a popular, well-established mechanism

by which pediatric surgeons (often from HICs) directly contribute to surgical care delivery in LMICs over a short period of time.[55] Such missions can also be highly cost-effective, as reported by Davis et al.,[56] who calculated a cost-effectiveness $385 USD per DALY averted for a 1 week pediatric neurosurgical mission in Guatemala. Smile Train, a global charity, which operates surgical missions for cleft lip and palate, operates impressively cost-effective surgical missions which cost USD $72–$134 per DALY averted on average.[48]

While surgical missions represent an effective and important means of delivering care in the short term, this mechanism of care delivery does not address systemic barriers to accessible pediatric surgical care in LMICs, nor does it generally permit for longer-term or multi-stage surgical intervention. Developing and sustaining domestic pediatric surgical capacity within LMICs is therefore a critical long-term priority, and a number of approaches to doing so have shown promise. Local treatment centers have been successfully developed under the auspices of international aid organizations, grassroots initiatives in LMICs, and faith based organizations.[18,57] Collaborative international quality improvement programs can significantly improve patient outcomes at healthcare facilities in LMICs.[58] Visiting surgeons may also contribute to cultivating domestic pediatric surgical capacity by concurrently training local practitioners as they deliver care. This approach mitigates the "brain drain" which arises when practitioners from LMICs train and then ultimately practice abroad, and enables local providers to become adept at practicing within the local resource context.[47,59]

The growth of domestic pediatric surgical workforces in LMICs will be central to increasing pediatric surgical capacity. In the context of the current dearth of trained pediatric surgeons in LMICs, providers with minimal pediatric surgical training may be relied upon to perform pediatric surgery, and trained pediatric surgeons may be responsible for millions of children with no other access to pediatric surgical services.[54,60] In a recent study by Chirdan et al., 24.4% of African pediatric surgeons received their primary training in Europe or North America. Of the 75% of African pediatric surgeons who trained primarily in Africa, 75% practiced clinically outside of Africa for a short period of time. About 45% of pediatric surgical programs had no or irregular trainees per training session and 52% had only one or two trainees per training session.[54] These findings suggest two complimentary, overarching strategies by which to cultivate the growth of the pediatric surgical workforce: (1) to support and expand pediatric surgical training opportunities within LMICs and (2) to expand and underwrite international training opportunities for aspiring pediatric surgeons from LMICs, when no such local opportunities exist. Regional treatment centers can play an important role in providing training opportunities for providers from nearby countries with limited or no domestic access to such training.[61] Collaborative partnerships between surgical training programs in HICs and LMICs represent another mechanism which helps to bolster the growth of the surgical workforce within LMICS, as these programs often provide reciprocal training opportunities for residents and surgeons from both countries. Programs such as those at multiple University of California campuses, Vanderbilt, Iowa University of British Columbia and Wisconsin serve as examples of such collaborations.[13] To the authors' knowledge, only a few pediatric surgical fellowship programs have yet established comparable international partnerships; such collaborations represent a ripe opportunity to specifically train global pediatric surgeons.

Pediatric surgeons at all levels of training can also support and contribute to global pediatric surgery via research. Further research on the incidence and prevalence of pediatric surgical disease, the true disease burden in terms of morbidity and mortality, the disease burden that can be averted by pediatric surgical intervention and the effectiveness and cost-effectiveness of various pediatric surgical services is desperately needed.[9,11,45] Such research will both inform clinical practice, and serve as powerful tool for ongoing advocacy.

Conclusion

Congenital anomalies are responsible for a substantial global burden of disease. Initial evidence supports pediatric surgery as an effective and cost-effective means to dramatically reduce the avertable suffering caused by congenital anomalies in LMICs. As with the larger field of global surgery, global pediatric surgery is rapidly gaining recognition as a central part of child health development programming. The time for global pediatric surgery is now, and pediatric surgeons must continue to step up as leaders driving global pediatric surgery forward, via clinical, educational, and research contributions.

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ORIGINAL SCIENTIFIC REPORT

Inequitable Access to Timely Cleft Palate Surgery in Low- and Middle-Income Countries

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Abstract

Background Delayed cleft palate repair has significant implications for physical, mental, and social well-being and has been suggested to lead to an increased risk of infant and under-five mortality in low- and middle-income countries (LMICs).

Methods Using medical records from Operation Smile international programs taking place in eleven different LMICs between March and May 2014, we performed a logistic regression assessing the relationship between delayed surgery access, defined as primary palatoplasty presentation after 24 months of age, and GDP per capita across 11 countries.

Results Median age of presentation ranged from 13 to 24 months in upper-middle-income countries, 17 to 35 months in lower-middle-income countries, and 14 to 66 months in low-income countries. Our analysis demonstrated a 14 % increase in the odds of late surgery [OR = 0.88 ($P < 0.001$)] for every 1000 USD decrease of GDP per capita. In low- and lower-middle-income countries, this relationship was even stronger, with an OR of 0.59 ($P < 0.001$), indicating a 70 % increase in the odds of late surgery for every 1000 USD decrease in GDP per capita.

Conclusions There is a strong negative correlation between national income status and delayed access to primary cleft palate surgery, indicating a high degree of inequity in access to surgery, particularly in low- and lower-middle-income countries. As the importance of surgery in global health is increasingly recognized, an equity perspective must be included in the global dialog to ensure that the world's poor have fair and equitable access to essential surgical care.

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Introduction

Health inequity refers to imbalances in well-being and access to healthcare that are systematic, unfair, and socially produced [1]. These imbalances are generated from the unjust social and economic structures that divide groups within a population. The concept of health equity is rooted in the human right of every individual to the highest standard of attainable health [2]. The global health community is not unfamiliar with such disparities. Over 2.3

million people in low- and middle-income countries (LMICs) die from vaccine-preventable illnesses every year, a woman's risk of dying from complications of childbirth range from 1 in 3200 in high-income settings to 1 in 16 in certain areas of sub-Saharan Africa, and two billion people around the world currently lack access to basic health services [3, 4]. Promoting health equity centers on removing barriers to care for the most vulnerable populations and improving upon the social, economic, and political determinants of health. Vast improvements have been made by the global community in promoting equitable access to vaccination, HIV treatment and prevention, and maternal and child health services, but greater action is still necessary to support equitable access to surgery and to foster the goal of a "grand convergence" in Global Health 2035 [5, 6].

Termed "the neglected stepchild of global health," surgery and the burden of surgical disease are at present under-represented in the global health discourse [7]. Cleft lip and/or palate (CL/P) is a surgical condition of multifactorial etiology that disproportionately affects the poorest populations throughout the world. The prevalence of CL/P varies by region and global estimates range from 1 in 700 to 1 in 1000 live births worldwide [8, 9]. While infant mortality is only modestly affected by CL/P in high-income settings, studies have demonstrated high infant mortality rates in even isolated forms of this condition in Latin America, as well as up to a seven-fold increase in risk of neonatal death in China [9–11]. The impact of CL/P on infant mortality is presumed to be markedly higher in sub-Saharan Africa, where the risks of malnutrition, upper respiratory infections, and diarrheal illness may be further compounded by the birth defect [12]. Early identification of the condition and referral to nutrition counseling and surgery can, however, reduce the magnitude of these risks [13, 14]. For this reasons, cleft palate repair is classified as an essential surgical procedure by the World Health Organization.

Operation Smile, Inc. was founded in 1982 and is headquartered in Virginia Beach, VA. Operation Smile is a privately funded, international, nongovernmental organization that has provided reconstructive surgery to over 220,000 people in LMICs since its inception. The organization employs a locally integrated mission-based approach to reach patients in areas with limited surgical capacity. To better characterize existing disparities in access to surgery, as well as to assess the degree of inequity that exists related to CL/P care, we evaluated the relationship between access to cleft palate surgery and national economic indicators using data collected during reconstructive surgery missions conducted by Operation Smile in eleven different LMICs.

Material and methods

For this investigation, Operation Smile's medical records department provided depersonalized patient data from eleven surgical missions occurring between March and May 2014. These missions took place in Ghana, Ethiopia, Democratic Republic of Congo, and Madagascar in Africa; China and India in Asia; and Nicaragua, Bolivia, Paraguay, Peru, and Mexico in Latin America. Information regarding patient gender, age of presentation, screening diagnosis, proposed surgical repair, and documented operation were included. All patients and/or patient guardians were consented in their native language during screening for potential secondary uses of patient data and all patients who denied consent were excluded from this analysis. This study was also reviewed and approved by Operation Smile's Institutional Review Board.

Data from patients who presented with an unrepaired cleft palate, with or without cleft lip, were extracted from the dataset. Age of presentation for primary, unrepaired cleft palate was used as an indicator of access to palatoplasty. Age of presentation for cleft palate was used in this analysis because delayed provision has significant recognized implications for speech, development, and risk of infant mortality [14–16]. We specifically focused on cleft palate, with or without cleft lip, because this defect has greater established effects on morbidity and mortality [9]. Additionally, we used patient presentation data as opposed to operative records in order to prevent our indicator from being artificially inflated by other factors that may preclude surgery at the time of a patient's initial presentation. Such potential factors include the patient having concomitant anemia (Hgb < 10); the patient being younger than the minimum age for CLP/CP surgery as established in the Operation Smile standards of care (12 months for palatoplasty); or the sheer volume of presenting patients overwhelming the mission's operative capacity. The screening data was also verified by and reconciled with the proposed surgical plan listed in the screening records and documented operation provided, as available.

We first analyzed patient ages by country using descriptive statistics, calculating the median, 25th percentile, and 75th percentile. We additionally performed an analysis of variance, comparing presentation ages between the countries. These findings were also compared qualitatively by region, country income classification (e.g., low-income, lower-middle-income), and GDP per capita. Income categories were determined from 2014 World Bank designations [17]. Values for GDP per capita were obtained from the 2014 World Bank estimates in current USD [18]. We selected GDP per capita as the economic indicator in this analysis because it was the most universal and has been

shown to correlate well with other related measures such as Human Development Index (HDI) and Multidimensional Poverty Index (MPI) [19, 20].

Next, using logistic regression, we calculated the odds of late primary surgery presentation within the study countries and its relationship to GDP per capita. Although there is no definitive consensus regarding the optimal age of cleft palate surgery, surgical intervention is generally recommended by 12–18 months of age, and before 24 months, in order to prevent poor speech and functional outcomes [21–24]. Therefore, we defined "late surgery" as cleft palate presentation later than 24 months. We additionally included gender and gender-country interaction terms in our analysis to evaluate and account for the potential effects of gender on this relationship. Inclusion of gender in the final model was determined based on Akaike's information criterion (AIC), a common statistical tool to evaluate model fit. Gender-interaction terms were evaluated as well using the Wald test. We checked and evaluated the model results using a series of diagnostic tests to check our regression, including analyses of Pearson's residuals, leverage, and influence, additionally assessing the effects of identified outliers on our results. Last, recognizing that there is likely a minimum, natural rate of late surgery irrespective of other external factors and that the impact of economic status would potentially diminish at higher income levels, we repeated the regression excluding upper-middle-income countries. All statistical analyses we completed in Stata IC13 (Statacorp, 2013). $P < 0.05$ was considered significant.

Results

Patient ages at time of initial presentation for palatoplasty varied widely between and within countries (see Fig. 1). Overall, the youngest age of presentation was less than 1 week old and the oldest was 69.54 years of age. Median ages of presentation ranged from 13 to 24 months in upper-middle-income countries, 17 to 35 months in lower-middle-income countries, and 14 to 66 months in low-income countries (see Table 1). Countries in Africa had relatively higher median ages of presentation as compared to those is Asia and Latin America. Analysis of variation indicated statistically significant variation across the study countries ($P < 0.001$).

Logistic regression identified a statistically significant relationship between the odds of late surgery and GDP per capita (see Table 2). Including all study counties, the odds ratio (OR) was found to be 0.88 (95 % CI 0.85–0.93), indicating a 12 % reduction in the odds of late surgery for every 1000 USD increase in GDP per capita or, conversely, 14 % increase in odds for every 1000 USD decrease in GDP per capita (see Table 2). Gender was excluded from the model because its inclusion resulted in a higher AIC. Gender-interaction terms were similarly excluded as they were found not to be significant or improve the model fit. One outlier was identified with high levels of influence, as measured by both change in Pearson's Chi-squared and change in beta vector, Mexico. After removing the Mexico data from the regression, the OR was found to be even more significant [OR = 0.75 ($P < 0.001$)]. No other evidence of bias or error was detected in our analysis.

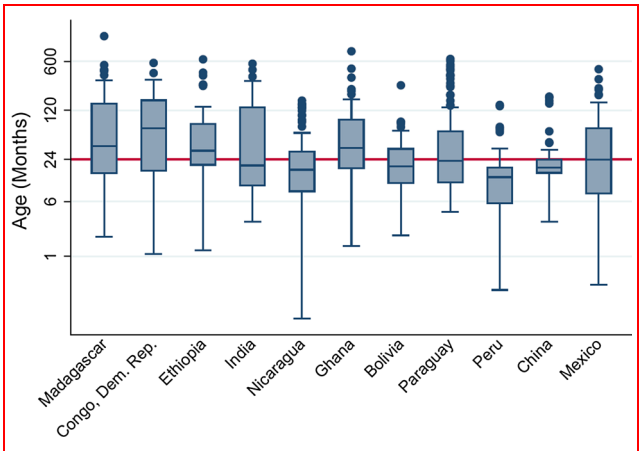

Fig. 1 Distributions of age at time of cleft palate presentation by country

When considering only low-income and lower-middle-income countries, this relationship was found to be markedly stronger. Excluding higher-middle-income countries yielded an OR of 0.59 (95 % CI 0.48–0.72), signifying a 70 % increase in odds of late surgery for every 1000 USD decrease in GDP per capita. Gender and gender-interaction terms were also excluded from this model by AIC and Wald tests. We did not identify any evidence of bias in our additional analyses of this model but one outlier was detected by change in Pearson's Chi-squared, Nicaragua. However, excluding the Nicaragua data did not remarkably impact our regression [OR = 0.64 ($P < 0.001$)].

Discussion

This investigation identified a significant negative correlation between GDP per capita and timely presentation for cleft palate surgery. According to our findings, those in lower-income countries are significantly less likely to access timely surgery and will accordingly endure the burden and complications of cleft palate for longer periods of time without operative repair. Our analysis indicated that in LMICs for every 1000 USD decrease in GDP per capita individuals with cleft palate faced a 14 % increase in the

Table 1 Descriptive statistics of age of presentation for palatoplasty by country

Country	Income classification*	GDP per capita (USD)	Median age (months)	Lower limit (25 %)	Upper limit (75 %)
Madagascar	LIC	463	36.62	14.79	144.99
Congo, Dem Rep	LIC	484	66.41	16.60	166.92
Ethiopia	LIC	505	13.82	19.99	76.11
India	LMIC	1498	19.56	10.19	131.87
Nicaragua	LMIC	1851	16.96	8.38	31.04
Ghana	LMIC	1858	34.92	17.88	88.50
Bolivia	LMIC	2868	18.90	11.08	33.86
Paraguay	LMIC	4265	22.85	11.18	60.20
Peru	UMIC	6662	13.35	5.69	18.20
China	UMIC	6807	18.22	15.37	23.61
Mexico	UMIC	10,307	23.64	7.86	66.54

* Income classification as designated by the World Bank [17]

LIC lower-income country; *LMIC* lower-middle-income country; *UMIC* upper-middle-income country)

Table 2 Results of the logistic regression of the odds of late surgery relative to GDP per capita

	Variable	Value	*P* value	Lower limit (95 % CI)	Upper limit (95 % CI)
All countries:	OR	0.88	<0.001	0.85	0.93
	Constant	1.34	0.004	1.10	1.63
Low- and lower-middle-income countries:	OR	0.59	<0.001	0.48	0.72
	Constant	2.25	<0.001	1.66	3.05

odds of late surgery. This relationship was particularly marked in low- and lower-middle-income countries, where our analysis identified an OR of 0.59, signifying a 70 % increase in the odds of late surgery for every 1000 USD decrease in GDP per capita. Together, these findings illustrate the significant connection between of national income and economic factors and access to cleft palate surgery, especially in low-income and lower-middle-income countries. Although this relationship has been suggested anecdotally, the degree of this relationship has not been well appreciated in the literature prior to this investigation.

There are a few notable limitations to this analysis. First, patient age at primary cleft palate presentation was used instead of age of palatoplasty itself. As described in the methods section, this was done to prevent other factors that may delay surgery from biasing our results. The age data used here, therefore, represent relatively conservative measures of timely palatoplasty access. Next, we used GDP per capita as our measure of economic status. As an aggregated national indicator, however, this does not account for internal variability in income status. This consideration is especially notable given the relatively high index of inequality in most LMICs and that the patient populations encountered on Operation Smile missions are largely from disadvantaged backgrounds [25]. The true degree of inequality in access to palatoplasty is likely even greater both between and within the countries considered here. This unaccounted for internal variation likely resulted in Mexico's outlier status in our analysis. Third, patients and families who did not consent for their information used in research were excluded from the study. Although this only represented a relatively small number of cases, this is a potential source of bias in our findings. Last, only eleven LMICs were included in this analysis, thereby limiting the statistical analysis and precluding any conclusions being drawn relative to high-income countries (HICs). The fact that the relationship between late surgery and GDP per capita was strongest in lower-income countries suggests that there may be a threshold at which national income status no longer affects timely cleft palate surgery access. Future studies could potentially include a larger number of countries across all income levels. This would lead to even more robust statistical conclusions and would also enable researchers to evaluate the potentially changing relationship across different national income classifications.

Regardless of these considerations, the findings of this investigation support the existence of a significant negative correlation between GDP per capita and cleft palate

surgery access in LMICs, the magnitude of which is likely only underestimated here. Delayed access to palatoplasty, like many other types of surgery, translates to significant negative sequelae and an increased burden of disease, disproportionately affecting those in low-resource settings. Cleft palate repair is generally recommended for infants born with cleft palate by 12–18 months of age [21–23]. In the U.S., most children with cleft palate receive surgery before 12 months of age [24]. As demonstrated by research in high-income countries, in addition to physical morbidity and the risks of infection, malnutrition and death, unrepaired cleft palate can have major negative implications for speech, hearing, self-esteem, and psychological development, which can lead to long-lasting adverse outcomes for social integration [15, 16]. Unrepaired CL/P often results in poor school attendance, low employment rates, and frank social rejection [26]. Further research is necessary to explore the risks associated with delayed access to palatoplasty in LMICs, which are likely only compounded by the associated resource limitations. Further study is also essential to begin to characterize patterns of cleft-related mortality in LMICs to help guide additional intervention programs. Additionally, the environmental risk factors associated with CL/P (maternal malnutrition, exposure to pollution and smoking, social stressors, and poverty in general) mirror the very social determinants of health and infants born with CL/P represent a distinctly at-risk subset of the population [2, 15, 27].

An equity-based approach to global health requires a pro-poor focus on the most vulnerable populations [9, 28]. While CL/P requires an interdisciplinary approach to care, surgery is ultimately the definitive treatment. Poor access to surgery results in the increased marginalization of this already disadvantaged population, creating an inescapable, cyclical trap of inequity [29]. Conversely, access to safe, well-timed surgical repair for CL/P positively effects a person's overall health achievement, increasing the physical, mental, and social well-being of the individual [29].

These findings furthermore support the presence of a greater inequity in access to surgery worldwide [30]. Surgical conditions are estimated to account for 11 %, and potentially as high as 30 %, of the global burden of disease [31]. Only 3.5 % of all surgical procedures take place in lower-income countries, while they account for greater than one-third of the global population [32]. And yet, as the "neglected stepchild of global health," limited attention has been paid to surgery outside of obstetric and injury care [6, 7]. Augmented support at both the country and international levels are essential to erase the inequities that currently affect access to surgery in LMICs [5]. Effective solutions to improve access to surgical care will undoubtedly be responsive to the patient's perspective, deeply rooted in context, resource availability, and local health system priorities and a standardized/undifferentiated approach will not be feasible. However, initial interventions to promote improved access to surgery may take the form of increased surgical training opportunities, construction of operating facilities, mission-based efforts, decreasing the barriers that patients face in accessing care and other capacity building and stop-gap interventions [33, 34]. As stated by Paul Farmer and colleagues, "what branch of medicine or public health is not forced to confront the growing outcome gap that promises to shield the privileged, while the world's bottom billion continue to die from readily preventable or treatable disease" [35]. For infants born with CL/P and other vulnerable populations living in LMICs, surgery is an essential component of the human right to the highest standard of attainable health and demands a place in the movement for health equity [36].

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ORIGINAL SCIENTIFIC REPORT

Patient Barriers to Accessing Surgical Cleft Care in Vietnam: A Multi-site, Cross-Sectional Outcomes Study

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Abstract

Background Most people who lack adequate access to surgical care reside in low- and lower–middle-income countries. Few studies have analyzed the barriers that determine the ability to access surgical treatment. We seek to determine which barriers prevent access to cleft care in a resource-limited country to potentially enable barrier mitigation and improve surgical program design.

Methods A cross-sectional, multi-site study of families accessing care for cleft lip and palate deformities was performed in Vietnam. A survey instrument containing validated demographic, healthcare service accessibility, and medical/surgical components was administered. The main patient outcome of interest was receipt of initial surgical treatment prior to 18 months of age.

Results Among 453 subjects enrolled in the study, 216 (48%) accessed surgical care prior to 18 months of age. In adjusted regression models, education status of the patient's father (OR 1.64; 95% CI 1.1–2.5) and male sex (OR 1.61; 95% CI 1.1–2.4) were both associated with timely access to care. Distance and associated cost of travel, to either the nearest district hospital or to the cleft surgical mission site, were not associated with timing of access. In a sensitivity analysis considering care received prior to 24 months of age, cost to attend the surgical mission was additionally associated with timely access to care.

Conclusions Half of the Vietnamese children in our cohort were not able to access timely surgical cleft care. Barriers to accessing care appear to be socioeconomic as much as geographical or financial. This has implications for policies aimed at reaching vulnerable patients earlier.

Jordan W. Swanson and Caroline A. Yao have contributed equally to this work.

This study has 8 authors. The international, multi-site nature of this study involved surgeons, statisticians, and global health researchers from several sites in all key phases of the study. Each meets WJS criteria as an author.

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Introduction

Among the five billion people who lack adequate access to surgical care, most reside in lower- and lower–middle-income countries [1]. Growing evidence characterizes the degree of suffering, disability, mortality, and persistent

poverty that propagate in individuals and communities that are beyond the reach of surgical treatment [1]. People who are the poorest, live rurally, and are most marginalized from society are thought to be the most disenfranchised [2]. Surgical treatment is increasingly found to be cost-effective in reducing disability, particularly compared to other medical interventions [3, 4]. However, a combination of structural, financial, and cultural barriers is thought to prevent both access to and delivery of surgical care [5]. Understanding which factors most prominently hinder access to surgical care, and the interrelationship between factors, is a crucial prerequisite to counteracting them.

Congenital anomalies are responsible for a staggering 57.7 million disability-adjusted life year (DALYs) lost globally with 94% occurring in lower- and middle-income countries (LMICs) [6–8]. Cleft lip and palate constitute the most common congenital anomalies, occurring in one of every 300–500 births [9]. Surgical treatment is highly successful at correcting the impaired speech, oral-lingual dysfunction, and stigmatizing appearance of cleft lip and palate. Repair is cost-effective, at an average USD48 per DALY averted [4, 10]. Cleft lip and/or palate repair is ideally performed once optimal nutrition has been assured, in one or two stages, and between 3 and 18 months of age. Because language acquisition begins in the first year of life, palatal repair after 18 months of age is associated with inferior speech outcomes in the form of compensatory articulations that can persist even after late surgical repair [11]. However, a large portion of children born with cleft deformities in LMICs do not receive treatment, and among those who do, many suffer the poorer outcomes of late treatment [12].

Two recent studies of patients [13] and providers [14] in LMICs illustrated that barriers to cleft care are perceived to be multi-dimensional and widespread; however, neither study was designed to assess the specific influence of certain barriers on access and outcomes. In order to better characterize barriers to surgical cleft treatment in a lower-resource setting, and the relative impact of each, we investigated children and families accessing cleft care at multiple sites throughout Vietnam. Four barrier types were considered: patient characteristics, family education and socioeconomics, geographic location, and cleft treatment site features. The outcome of interest was successful access of cleft surgery prior to 18 months of age.

Materials and Methods

Setting and Study Sources

In this cross-sectional study, surveys were administered to families who attended surgical cleft care missions in Vietnam, a lower–middle-income country, in November 2014 [15, 16]. Operation Smile Vietnam provides cleft care through both year-round treatment centers and medical missions within the country. Data collection was performed in five cities: Hanoi, Nghe An, Hue, Ho Chi Minh, and An Giang. Included subjects were families in which a member had a diagnosis of cleft lip and/or palate and resided in Vietnam. Each of the mission sites used in the study was a regular mission site for Operation Smile Vietnam, with long-term hospital partnerships and regular surgical missions being held generally semi-annually or annually at each site.

A survey instrument was designed to assess patient demographic and clinical characteristics, family socioeconomics, geographic factors, and cleft treatment site features that may constitute barriers to accessing cleft and broader surgical care (Fig. 1). Multiple indicators were employed to assess varying dimensions in which barriers may impact family care-seeking decision making. For example, three measures of geographic barriers to care—measured distance, time to travel that distance, and reported out-of-pocket costs of traveling that distance—were evaluated and were each assessed with respect to both the nearest hospital and the cleft mission site. Demographic and healthcare accessibility components were adapted from the validated *Multi-Country Survey Study* and *World Health Survey* of the World Health Organization health system responsiveness questionnaires [17]. Questions pertaining to patient medical and surgical history were adapted from the *International Family Study*, an epigenetic cleft study [18].

Local, bilingual (English–Vietnamese) medical and dental students were trained as study administrators through a comprehensive course that addressed clinical background, standards of data collection, professionalism, and cultural sensitivity. At each mission site, families were randomly enrolled based on the availability of study administrators. In providing consent, families were informed that neither participation nor opting out would impact care received. The survey was administered in a confidential setting to an authority figure (generally a parent, relative, or close friend) in the household over 17 years of age if the patient was a minor.

Patient transport costs were self-reported and were specified to include direct costs only of transporting the patient and one caregiver/guardian, but not indirect costs (e.g., lost wages) of attending the mission. Patient transport was not routinely arranged by mission staff, and most distant families used public buses. Food and lodging for the patient and one caregiver at the mission site peri-operatively were provided, and families were informed of this coverage in advance. Although transport cost reimbursement was provided to some patients *ad hoc*, this occurred after the study questionnaire was completed and was not a policy during the mission.

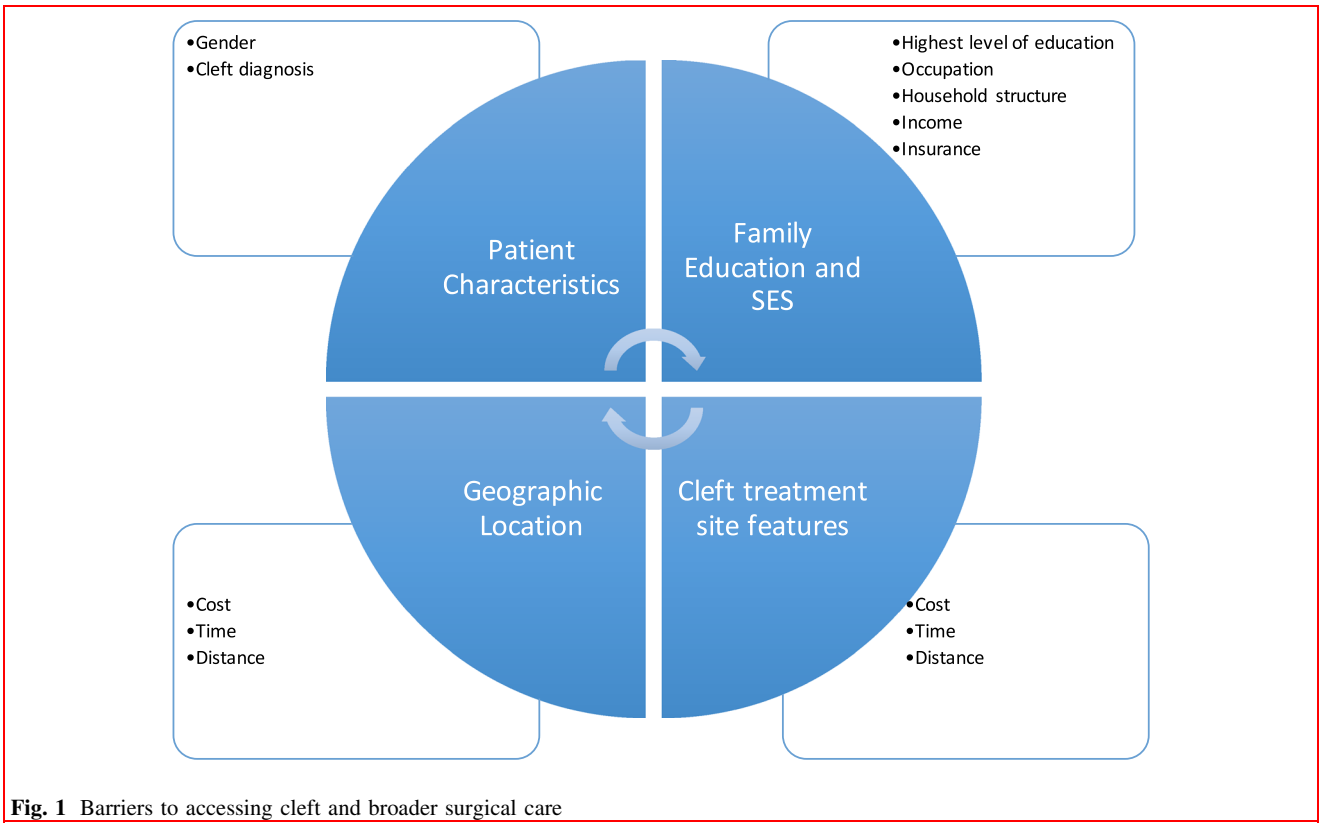

Fig. 1 Barriers to accessing cleft and broader surgical care

The Ethical Review Boards of the Vietnam Ministry of Health and the University of Southern California approved this study.

Data and Statistical Analysis

Age at initial surgery was ascertained for patients who had received previous surgical treatment, and their current age at presentation to the mission was used for surgical candidates who were previously untreated.

Descriptive statistics were calculated and evaluated using 18 months as a cutoff for initial surgery presentation, and 24 months was also evaluated to assess the sensitivity of the data. Chi-squared tests for proportions were used to determine differences in prevalence of factors of interest among the groups. The cross-sectional data were analyzed through the comparison of odds ratios (ORs) in both unadjusted and adjusted models. The adjusted model accounted for father's education as a proxy for socioeconomic status, distance to the nearest hospital (a factor previously reported as a barrier [13, 19]), and cost to attend the mission, which is reimbursed by Operation Smile in certain cases. Some continuous variables were dichotomized to facilitate analysis, after preliminary assessment of logical breakpoints. Analyses used a two-sided α level of 0.05 (all CIs reported at 95%) and were done with SAS 9.3 (SAS Institute, Cary NC). Finally, in order to assess for any confounding factors between patients presenting for their first surgery and those who had initial repair previously (e.g., household characteristics changed in the interim), each cohort was then analyzed separately and the results compared.

Results

Among 884 total households presenting to a cleft mission site, 453 (51%) households were randomly enrolled in, and all 453 completed the study. Two hundred and sixty patients were male (58%). An average of 91 patients was evaluated at each site (range 66–136). Subjects most commonly were diagnosed with cleft lip and palate ($n = 219$, 48%), followed by isolated cleft palate ($n = 123$, 27%) and then isolated cleft lip ($n = 100$, 22%). Two hundred and seven patients (46%) were receiving their initial surgery, and 246 patients (54%) had previously received surgery. A similar proportion of patients received their initial surgery before 18 months of age in the first (94, 45%) and second (125, 51%) cohorts ($P = 0.26$.) The mean and median age of first surgery were comparable in the first (2.6; 1.7 years) and second (3.8; 1.4 years) cohorts. Among those who had received previous surgery, a mean 3.8 years and median 2.2 years had elapsed since their first surgical treatment.

In univariate analysis, patient factors of cleft lip ± palate diagnosis and male sex, as well as paternal education of greater than secondary school, were associated with timely surgery (Tables 1, 2; Figs. 2, 3). Similarly, living within 10 km of a hospital and hearing about the cleft mission through family or social media channels were associated with timely surgery (Tables 3, 4; Figs. 4, 5).

Adjusted Factor Model

Potential barriers to accessing care were modeled and adjusted for father's education, distance to the nearest hospital, and cost to mission (Fig. 6). Males were almost twice as likely as females to access surgical treatment prior to 18 months [OR 1.7 (1.1,2.7)] and prior to 24 months [OR 2.0 (1.3,3.2)]. A patient's father being educated beyond secondary school was associated with increased odds of surgical treatment prior to 18 months [OR 1.8 (1.1,2.8)] and prior to 24 months [OR 1.9, (1.2,3.1)]. A parent presenting with their child to the mission was associated with their child being more than twice as likely to present for surgery prior to both 18 months [OR 2.1 (1.1,4.2)] and 24 months of age [OR 2.7 (1.4,5.2)]. Neither paternal nor maternal occupation was associated with prompt access.

Patient families living greater than 10 km from the nearest hospital were less likely to present for treatment before 18 months of age [OR 0.6 (0.4,0.9)] compared to those living within 10 km of a hospital. However, neither time of travel nor cost associated with travel to the nearest hospital was associated with timing of treatment. The travel time, cost, and distance to the mission site were not associated with age that the patient was treated. Learning about the mission from family or friends was associated with prompt treatment prior to 18 months [OR 2.3 (1.1,4.7)] and 24 months of age [OR 2.6 (1.2,5.5)], compared with media/Internet or government/national organizations.

In a subgroup analysis of only patients presenting for their initial surgical treatment, three factors were found to significantly influence timeliness of care—male gender [OR 2.3 (1.2,5.0)], paternal education [OR 2.9 (1.4,5.8)], and parental guardian [OR 3.2 (1.0,9.8)]. Distance to nearest hospital [OR 0.87 (0.7,1.2)] and channel through which heard about the mission [OR 2.2 (0.9,5.6)], the other two significant factors in the combined analysis, trended toward similar findings, but were not significant in this smaller sample.

Discussion

Surgical treatment is most effective when it is performed in a timely fashion. Our understanding of barriers to accessing surgical care is not complete unless it incorporates surgical outcomes. Timely surgical treatment is particularly important in low- and middle-income countries, where constrained resources and follow-up hinder rectification of suboptimal outcomes. This study was undertaken to better understand how patient characteristics and care-seeking behaviors may predispose to poorer expected outcomes. Understanding patient perspectives of care accessibility must accompany increasing care availability, to prevent

Table 1 Characteristics of patients at initial treatment

	Age that child received surgery					
	<18 months	≥18 months	*P* value	<24 months	≥24 months	*P* value
Gender ($n = 448$)						
Male	140 (65%)	120 (52%)	**0.005**	166 (63%)	94 (51%)	**0.0067**
Female	76 (35%)	112 (48%)		96 (37%)	92 (49%)	
Diagnosis*						
Cleft lip only	60 (28%)	40 (18%)	**0.011**	67 (26%)	33 (18%)	**0.066**
Male	*40 (63%)*	*24 (37%)*	*0.5*	*45 (70%)*	*19 (30%)*	*0.35*
Female	*20 (56%)*	*16(44%)*		*22 (61%)*	*14 (39%)*	
Cleft palate only	35 (16%)	88 (39%)	**<.0001**	47 (20%)	76 (42%)	**<.0001**
Male	*22 (41%)*	*32 (59%)*	*0.008*	28 (52%)	26 (48%)	*0.006*
Female	*13 (19%)*	*56 (81%)*		19 (28%)	50 (72%)	
Cleft lip and palate	121 (56%)	98 (43%)	**0.008**	143 (55%)	76 (42%)	**0.008**
Male	*77 (56%)*	*61 (44%)*	*0.71*	84 (61%)	54 (39%)	*0.7*
Female	*42 (53%)*	*37 (47%)*		46 (58%)	33 (42%)	

Statistically significant values are given in bold ($p < 0.05$)

Italic values indicate subgroup analysis

Table 2 Family and socioeconomic characteristics of subjects

	Age that child received surgery					
	<18 months	≥18 months	*P* value	<24 months	≥24 months	*P* value
Mother more than secondary school						
No	90 (41%)	110 (50%)	0.074	108 (41%)	92 (53%)	**0.0153**
Yes	127 (59%)	110 (50%)		155 (59%)	82 (47%)	
						$N = 437$
Father more than secondary school						
No	81 (39%)	111 (50%)	**0.0265**	99 (39%)	93 (52%)	**0.0077**
Yes	126 (61%)	112 (50%)		153 (61%)	85 (48%)	
						$N = 430$
Father occupation						
Farming	109 (54%)	134 (64%)	0.141	132 (54%)	111 (66%)	**0.0434**
Government/professional/military	16 (8%)	14 (7%)		20 (8%)	10 (6%)	
Labor, skilled, self-employed, service	76 (38%)	62 (30%)		92 (38%)	46 (28%)	
						$N = 411$
Mother occupation						
Farming	108 (51%)	132 (60%)	0.2017	133 (51%)	107 (61%)	0.193
Government/professional	21 (10%)	13 (6%)		24 (9%)	10 (6%)	
Work from home/unemployed	28 (13%)	27 (12%)		34 (13%)	21 (12%)	
Labor/service	56 (26%)	49 (22%)		68 (26%)	37 (21%)	
						$N = 434$
Guardian relationship						
Parent	192 (88%)	192 (83%)	0.0852	234 (89%)	150 (81%)	**0.0135**
Other	25 (12%)	40 (17%)		29 (11%)	36 (19%)	
						$N = 449$
Annual household income VND ($USD)						
<40,000,000 ($1780)	45 (24%)	51 (26%)	0.9134	55 (24%)	41 (26%)	0.9496
20,000,000–40,000,000 ($890–$1780)	58 (31%)	56 (28%)		67 (30%)	47 (30%)	
40,000,001–60,000,000 ($1780–$2670)	43 (23%)	44 (22%)		51 (23%)	36 (23%)	
>60,000,000 ($2670)	40 (22%)	46 (23%)		53 (23%)	33 (21%)	
						$N = 383$

Statistically significant values are given in bold ($p < 0.05$)

exclusion of those more marginalized from care in austere environments of prolific poverty.

Several key findings emerge from this study. First, only half of the patients received surgical treatment within the optimal window of timing. Second, patient gender and social factors such as parental education are strongly deterministic of ability to seek prompt care. Third, although geographic factors such as proximity to a district hospital influence access to care, they may be of smaller magnitude. And fourth, patient care-seeking behavior appears to be more influenced by communication methods that are family- and social-network-centric compared to more conventional means such as public or official notices.

The optimal timing of surgical intervention differs by illness; even non-acute congenital conditions warrant timely treatment. Obtaining good functional speech is predicated on early repair of a palatal cleft, and the expected outcome begins to deteriorate as early as 12 months of age, almost certainly by 18 months [20–22]. Similarly, an unrepaired cleft lip conveys functional disability (eating, speaking) and stigmatization hinders social integration, constituting a disability of 2.5–6.3 adjusted years [23]. Thus, cleft lip repair is generally recommended at or before 6 months of age [24]. For these reasons, the timing of initial cleft lip and/or palate treatment poses a useful indicator to evaluate barriers to surgical care in LMICs.

We found that males were 1.7 times more likely than females to attain initial cleft surgery by 18 months of age, an association that strengthened at 24 months of age. This parallels previous studies that found boys were brought in greater numbers for surgical assessment and received more

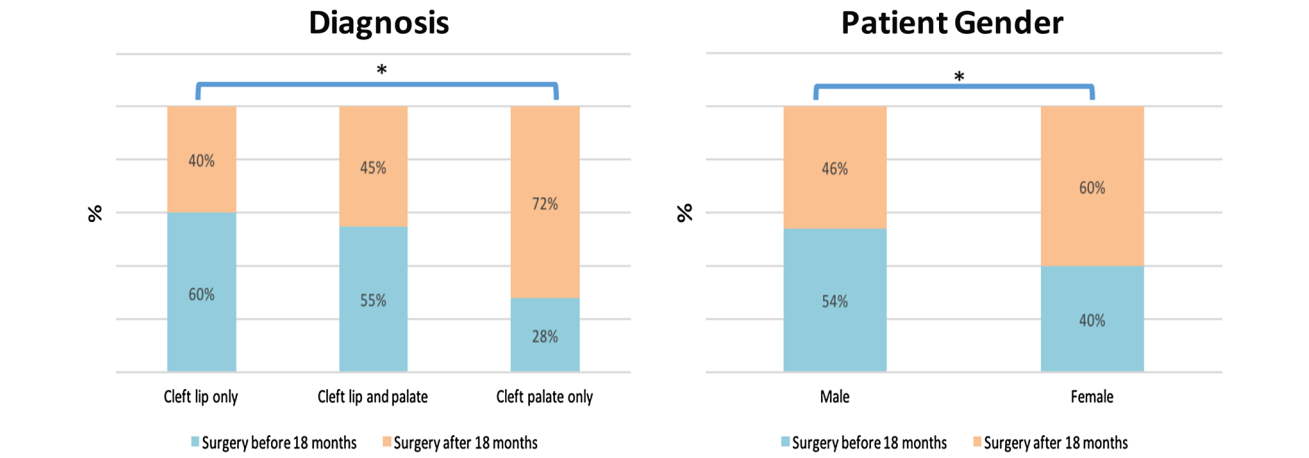

Fig. 2 Outcome of timely cleft surgery is associated with cleft diagnosis and patient gender

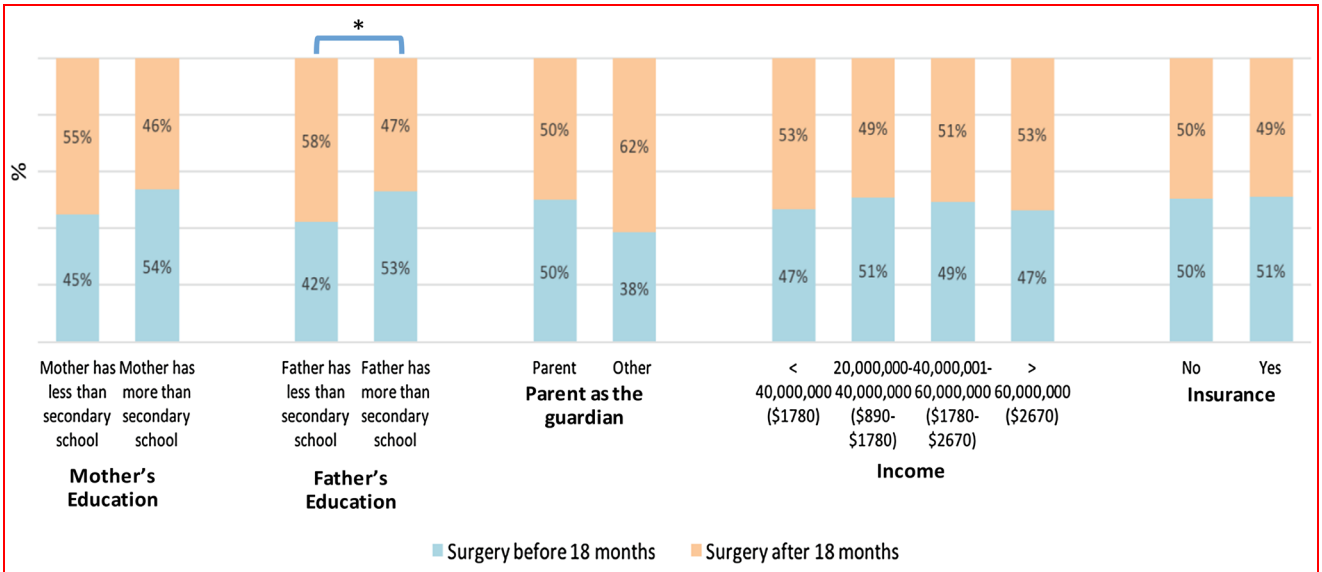

Fig. 3 Socioeconomic factors influencing timeliness of cleft care

surgical procedures than girls in LMIC settings [25, 26]. Although certain cleft deformity types are relatively more common in boys or girls [27], this would not be expected to influence optimal timing of presentation. In a subgroup analysis of patients with isolated cleft palate (Table 1), we noted an overall (male) sex ratio of 0.78 which is consistent with greater female incidence reported in the literature (male sex ratio of 0.76–0.79) [28]. However, we also noted significantly more males (41%) than females (19%) in this subgroup receiving timely care. This suggests that females with isolated cleft palates may be presenting for care in proportional numbers to males, but do so in a significantly delayed fashion. The factors causing this gender-based disparity in access are not clear from this study. Direct evidence of relative neglect in access for female children to health care and hospital admission has been identified in LMIC settings [29, 30]. Sen argues that the "missing women"—girls should biologically outnumber boys, but by age five, particularly in certain Asian and North African countries, they do not—most likely perish at the hands of engrained gender-preferential distribution of limited health, education, and nutritional resources [31].

Physical proximity to the nearest hospital was the singular geographic factor associated with prompt surgical treatment outcomes in this sample. This may support the emphasis placed on strengthening surgical care at the district hospital level by the recent *Lancet Commission on Global Surgery* [12, 19]. Nonetheless, because cleft

Table 3 Geographic characteristics and mission factors

	Age that child received surgery					
	<18 months	≥18 months	*P* value	<24 months	≥24 months	*P* value
Time to nearest hospital (h)						
Less than 30 min	95 (48%)	82 (38%)	0.052	113 (47%)	64 (37%)	0.0593
More than 30 min	105 (52%)	133 (62%)		130 (53%)	108 (63%)	
						$N = 415$
Distance to nearest hospital (km)						
0–10 km	121 (64%)	109 (53%)	**0.0391**	145 (63%)	85 (52%)	**0.0469**
10+ km	69 (36%)	95 (47%)		87 (38%)	77 (48%)	
						$N = 339$
Transport cost to nearest hospital						
0–50,000 VND	71 (45%)	76 (42%)	0.6521	85 (44%)	62 (42%)	0.6998
50,001+ VND	88 (55%)	104 (58%)		107 (56%)	85 (58%)	
						$N = 339$
Time to mission						
0–3 h	131 (61%)	130 (57%)	0.4028	151 (58%)	110 (60%)	0.7548
3+ h	84 (39%)	98 (43%)		108 (42%)	74 (40%)	
						$N = 443$
Distance to mission						
0–100 km	107 (61%)	103 (59%)	0.6166	125 (59%)	85 (61%)	0.7829
100+ km	68 (39%)	73 (41%)		86 (41%)	55 (39%)	
						$N = 351$
Transport cost to mission						
0–350,000 VND	71 (38%)	90 (46%)	0.0802	91 (40%)	70 (46%)	0.2296
350,000+ VND	118 (62%)	104 (54%)		139 (60%)	83 (54%)	
						$N = 383$
How family heard about mission						
Government, national organization	38 (27%)	65 (45%)	**0.004**	51 (29%)	52 (46%)	**0.0118**
Media/internet	53 (37%)	45 (31%)		62 (36%)	36 (32%)	
Family/friend	52 (36%)	35 (24%)		61 (35%)	26 (23%)	
						$N = 318$
City						
Ho Chi Minh City	36 (17%)	39 (17%)	0.0613	46 (17%)	29 (16%)	**0.0462**
Hue	36 (17%)	32 (14%)		43 (16%)	25 (13%)	
Nghe An	41 (19%)	65 (28%)		52 (20%)	54 (29%)	
An Giang	28 (13%)	37 (16%)		33 (13%)	32 (17%)	
Hanoi	77 (35%)	59 (25%)		90 (34%)	46 (25%)	
						$N = 450$

Statistically significant values are given in bold ($p < 0.05$)

surgery is not generally performed at district hospitals in Vietnam, it remains to be clarified why proximity to a district hospital improves access to cleft care—such as improved early diagnosis and referral through specialty services, or just a reflection of how close a family lives to the nearest city. That physical distance to the nearest hospital, but not travel time or associated cost, was associated with improved outcomes may suggest that it is the most deterministic factor of distance for family decision making or may implicate a physical "halo effect" of district hospital proximity, such as greater patient awareness or access to information. In addition to advocating for district hospital basic surgical care directly, our findings suggest that enhancing district hospital-based management of other surgical conditions (awareness, diagnosis, care protocols, referral) such as cleft may be a highly impactful complementary activity for overall health system strengthening, as proposed by McCord et al. [32].

Table 4 Odds of a participant receiving surgery before 18 or 24 months, unadjusted and adjusted ($N = 450$)

	Received surgery before 18 months		Received surgery before 24 months	
	Unadjusted OR (95% CI)	Adjusted[+] OR (95% CI)	Unadjusted OR (95% CI)	Adjusted[+] OR (95% CI)
Gender				
Female	1.00	1.00	1.00	1.00
Male	**1.72** (1.2, 2.5)**	**1.69* (1.1, 2.7)**	**1.69** (1.2, 2.5)**	**2.00** (1.3, 3.2)**
Mother more than secondary school				
No	1.00	1.00	1.00	1.00
Yes	1.41 (1.0, 2.1)	1.30 (0.7, 2.3)	**1.61* (1.1, 2.4)**	1.40 (0.8, 2.5)
Father more than secondary school				
No	1.00	1.00	1.00	1.00
Yes	**1.54* (1.1, 4.9)**	**1.77* (1.1, 2.8)**	**1.69** (1.2, 2,5)**	**1.94** (1.2, 3.1)**
Guardian relationship				
Non-parent	1.00	1.00	1.00	1.00
Parent	1.6 (0.9, 2.7)	**2.10* (1.1, 4.2)**	**1.94 ** (1.1, 3.3)**	**2.66** (1.4, 5.2)**
Time to nearest hospital (h)				
Less than 30 min	1.00	1.00	1.00	1.00
More than 30 min	**0.68* (0.5, 1.0)**	0.72 (0.4, 1.2)	0.68 (0.5, 1.0)	0.82 (0.5, 1.4)
Distance to nearest hospital (km)				
0–10 km	1.00	1.00	1.00	1.00
10+ km	**0.65* (0.4, 1.0)**	**0.57* (0.4, 0.9)**	**0.66* (0.4, 1.0)**	0.67 (0.4, 1.0)
Transport cost to nearest hospital				
0–50,000 VND	1.00	1.00	1.00	1.00
50,001+ VND	0.91 (0.6, 1.4)	1.0 (0.6, 1.7)	0.92 (0.6, 1.4)	1.05 (0.6, 1.8)
Time to mission				
0–3 h	1.00	1.00	1.00	1.00
3+ h	0.85 (0.6, 1.2)	0.82 (0.51, 1.3)	1.06 (0.7, 1.6)	1.16 (0.7, 1.9)
Distance to mission				
0–100 km	1.00	1.00	1.00	1.00
100+ km	0.9 (0.6, 1.4)	0.76 (0.5, 1.3)	1.06 (0.7, 1.6)	0.99 (0.6, 1.7)
Transport cost to mission				
0–350,000 VND	1.00	1.00	1.00	1.00
350,000+ VND	1.44 (1.0, 2.2)	1.52 (1.0, 2.4)	1.28 (0.9, 1.9)	1.34 (0.8, 2.1)
How family heard about mission				
Government, national organization	1.00	1.00	1.00	1.00
Media/internet	**2.02** (1.1, 3.5)**	1.62 (0.8, 3.2)	**1.76* (1.0, 3.1)**	1.42 (0.7, 2.8)
Family/friend	**2.50** (1.4, 4.6)**	**2.26* (1.1, 4.7)**	**2.39** (1.3, 4.4)**	**2.58* (1.2, 5.5)**

Statistically significant values are given in bold ($p < 0.05$)

[+] Model adjusted for: father's education, distance to nearest hospital, and cost to the mission site

* <.05; ** <.01

Interestingly, neither the distance, cost, or time to the surgical mission site appeared to influence outcomes, which may suggest that families have a high propensity to surmount the "delay to accessing care," [12] when they are aware of imminent treatment availability. Nonetheless, transportation and lodging costs for a mission may represent a modifiable barrier. Some surgical programs, either mission- or center-based, facilitate travel to an appropriate health facility, such as through reimbursement of travel costs [33].

One question raised by our results is whether surgical conditions such as cleft or cancer are better treated by different types of surgical system models than acute surgical conditions (e.g., cesarean section). Dare et al. [34] found increased mortality from acute abdominal conditions in India when patients lived more than 50 km from a well-

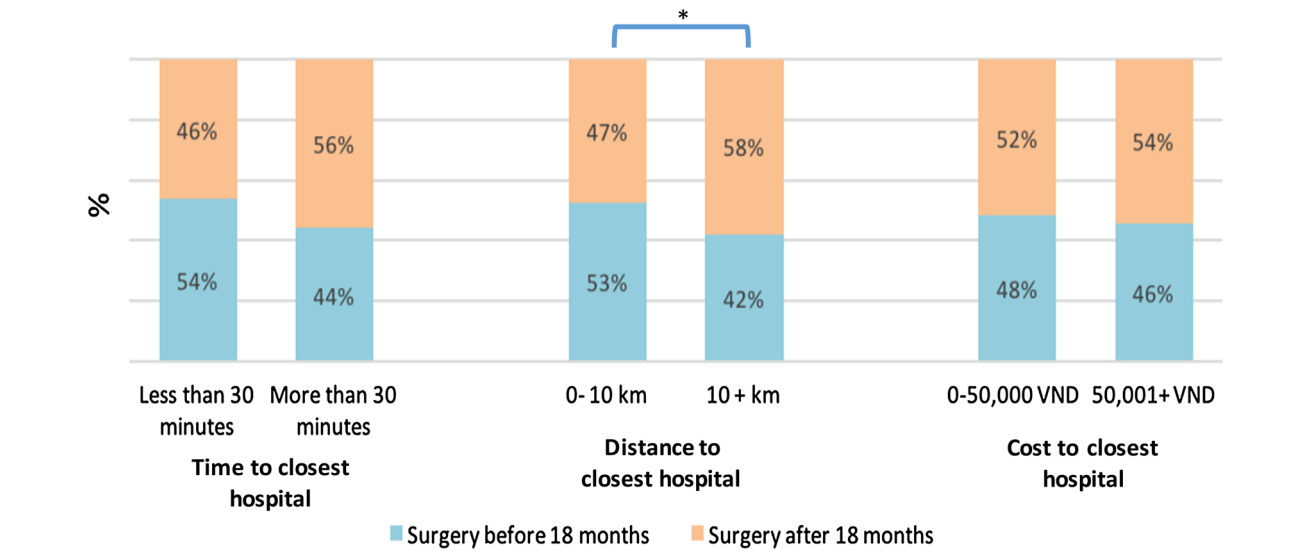

Fig. 4 Geographic factors of proximity to a healthcare facility influencing the timeliness of cleft care

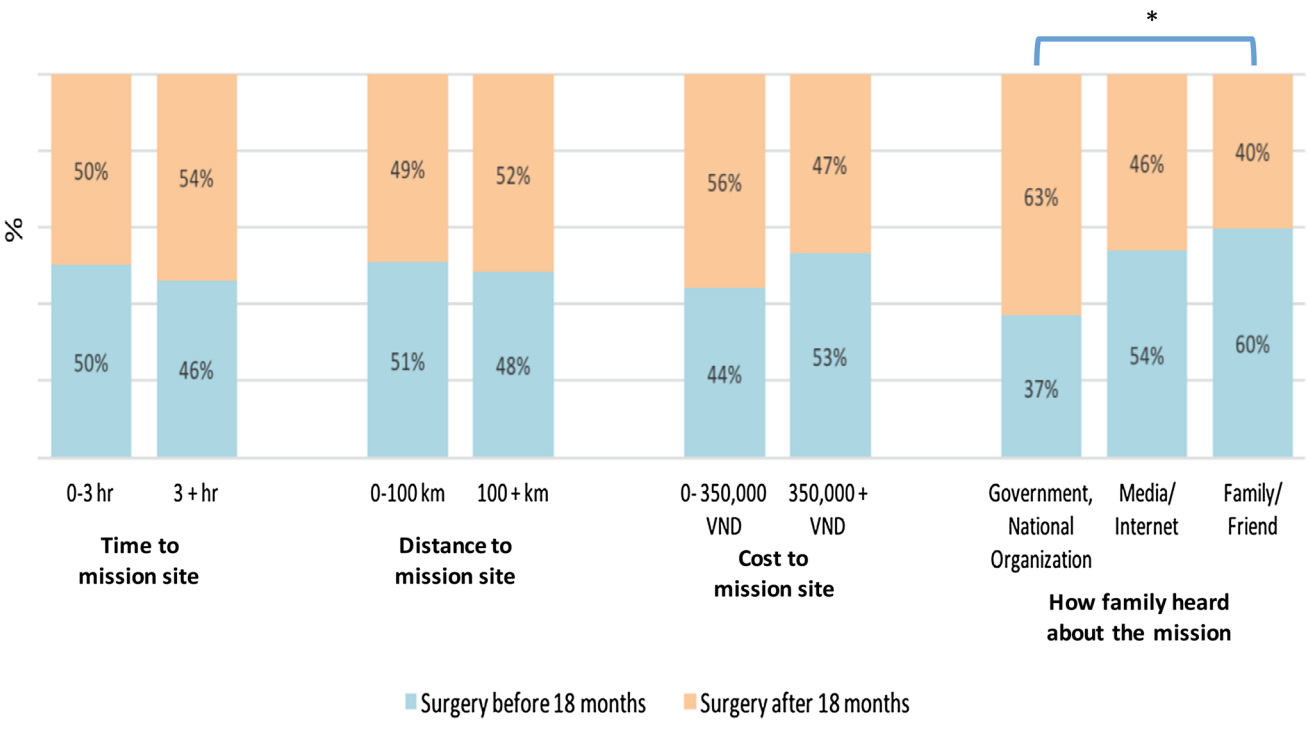

Fig. 5 Accessibility to the cleft surgical mission site and media channels through which family learned about the cleft mission influence timeliness of cleft care

resourced district hospital. However, no such relation was seen for deaths from non-acute surgical conditions, such as cancer. This may suggest that geographic proximity constitutes a smaller barrier for non-acute conditions, such as cleft, or it may also mask disability short of mortality. We were surprised that only one out of six indicators of geographic inaccessibility appeared to influence timeliness of care, and this may partly explain our findings in the context of studies that emphasize geographic barriers for acute conditions. Although not generally framed as "acute" or

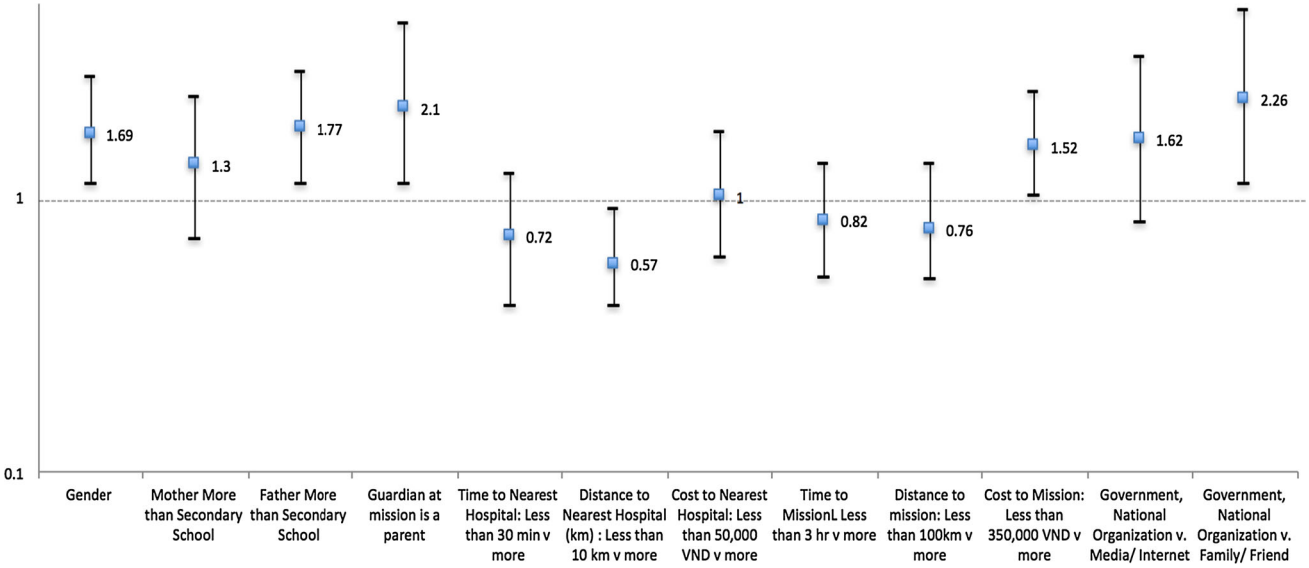

Fig. 6 Adjusted factor model accounting for multivariate barriers to care (odds ratio of timely access by factor)

"emergent" per se, timely treatment of clefts or cancer services are associated with better outcomes; likewise, such conditions benefit from more extensive preoperative workup and multidisciplinary team care [35]. Outreach programs to detect and refer these types of conditions earlier, as well as patient management networks, may demonstrate particular benefit for these and other surgical conditions.

Viewed in macro, the barriers faced by the families in this study attest to the interconnectedness of poverty and the challenging cultural context of disease. Among the 5 billion people who are estimated to lack access to surgery globally, basic subsistence needs such as food, housing, childcare, and transportation compete with healthcare priorities [12]. Likewise, limited knowledge, attitudes, and beliefs concerning cleft diagnosis and treatment influence the demand for care. Interestingly, a parallel study by our team assessed family perception of barriers to cleft care in a similar sample of Vietnamese people [13]. In it, high cost and distance travelled to obtain surgical care at the mission were the most commonly perceived barriers reported by patient families. However, neither factor was associated with a delay in obtaining surgical care, suggesting that these barriers are nonetheless overcome by affected families. The level of effort undertaken by the families who were able to overcome the barriers to accessing treatment is poorly understood.

Our study cohort reflected a mean income of 4.18 M VND (USD2400) per household, and most were farmers or unskilled laborers. This is lower than the GDP of VND 12.47 M (USD7180) per household and is likely representative of the rural communities that constitute the majority of Vietnam's population. This situates our study population among the middle of low-income countries by earning per capita, or conversely among the rural poor of lower–middle-income countries, and suggests its generalizability to these contexts [36].

The strengths of this study include the large sample size across five sites, the multiple types of barriers studied, and the objective outcomes analyzed. Several study limitations must be noted. First, the subjects reflect the cohort of patients who successfully sought out cleft care. Therefore, challenges facing these patients may not be representative of the community that was not able to "surmount" the barriers to presenting for care or to the small number estimated to receive paid treatment in private clinics. Second, all subjects were treated as a single cohort regardless of their individual cleft diagnosis; although level 3 evidence suggests cleft palatal repair superiority prior to 18 months of age, a definitive breakpoint for optimal lip repair is not defined. Nonetheless, given the extent of evidence for ongoing disability without lip repair, grouping this smaller subset of isolated cleft lip patients together with cleft palate patients was thought appropriate [10, 23, 37]. Similarly, acknowledging optimal palatal intervention by 18 months of age, and noting that patients with a cleft lip and palate are typically treated with lip repair first followed by staged palatal repair 3 months later, it could be suggested that 15 months of age be a more reasonable cutoff for optimal first surgery in this subgroup. Our decision to group these patients in a setting of generally delayed treatment in part reflected our goal of balancing cohorts with early and late surgery to best power our assessment of barriers. Finally, for patients who had received initial surgical treatment prior to the mission in

which the study was carried out, any factors that differed between the two settings were not captured. However, potential for confounding may be mitigated by the consistency of mission operation at the study sites, relatively short average elapsed time from initial surgical treatment to study participation, and low perceived degree of internal migration. And a separate cohort analysis among patients receiving initial treatment identified the same three barriers as the combined analysis; the other two factors trended toward significance, but did not achieve it likely due to the smaller sample size.

Some of the factors studied would be thought directly amenable to financial incentives (i.e., defraying transport costs) or investment in health infrastructure (i.e., expansion of district-level hospital care). However, the constellation of key barriers identified—being female, low parental education, accompaniment by a non-parent—appears more heavily rooted in social and cultural structure. Lasting alleviation of these factors may be possible with appropriate policy priorities over time. The state of Kerala, India, provides a hopeful example in which a strong education system and investment in health care have achieved high life expectancy in an otherwise very poor Indian state [31]. But what interventions might counter specific barriers to surgical access more expediently? A potentially comparable group of hard-to-reach individuals are those with chronic infectious disease, such as HIV or TB. This group also suffers from a non-acute ailment for which effective treatment is available, and is similarly characterized by poverty, homelessness, and youth [38]. Service-linking, relationship building, and advocacy have been among the most successful outreach components in affecting HIV treatment compliance. One practical realization of these components is through "accompaniment," in which a designated peer regularly accompanies the patient to appointments and treatment. They are able to provide support, while helping solve day-to-day barriers and reinforcing the commitment [38, 39]. Accompaniment by peer advocates, adapted to the cultural and geographic context, might facilitate improved cleft care outcomes. A pilot project in Honduras has recently adapted an accompaniment curriculum first developed by *Partners in Health* [40, 41] to cleft conditions and is utilizing parents of children with clefts in the role of peer advocate.

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Compliance with Ethical Standards

Conflict of interest We declare no competing interests, real or potential.

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Barriers to Reconstructive Surgery in Low- and Middle-Income Countries: A Cross-Sectional Study of 453 Cleft Lip and Cleft Palate Patients in Vietnam

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Background: Despite health system advances, residents of low- and middle-income countries continue to experience substantial barriers in accessing health care, particularly for specialized care such as plastic and reconstructive surgery.
Methods: A cross-sectional household survey of patients seeking surgical care for cleft lip and/or cleft palate was completed at five Operation Smile International mission sites throughout Vietnam (Hanoi, Nghe An, Hue, Ho Chi Minh City, An Giang, and Bac Lieu) in November of 2014.
Results: Four hundred fifty-three households were surveyed. Cost, mistrust of medical providers, and lack of supplies and trained physicians were cited as the most significant barriers to obtaining surgery from local hospitals. There was no significant difference in household income or hospital access between those who had and had not obtained cleft surgery in the past. Fewer households that had obtained cleft surgery in the past were enrolled in health insurance ($p < 0.001$). Of those households/patients who had surgery previously, 83 percent had their surgery performed by a charity. Forty-three percent of participants did not have access to any other surgical cleft care and 41 percent did not have any other access to nonsurgical cleft care.
Conclusions: The authors highlight barriers specific to surgery in low- and middle-income countries that have not been previously addressed. Patients rely on charitable care outside the centralized health care system; as a result, surgical treatment of cleft lip and palate is delayed beyond the standard optimal window compared with more developed countries. Using these data, the authors developed a more evidence-based framework designed to understand health behaviors and perceptions regarding reconstructive surgical care. (*Plast. Reconstr. Surg.* 138: 887e, 2016.)

Despite recent advances in health systems, people in low- and middle-income countries continue to face substantial barriers in accessing health care, particularly for specialized care such as surgery.[1] Access to surgical care was declared a global health priority by the United Nations Millennium Development Goals in 2008 and the World Health Organization Global Initiative for Emergency and Essential Surgical Care in 2005; both organizations identified the need to increase access to and improve standards for district-level surgical care in low- and middle-income

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A "Hot Topic Video" by Editor-in-Chief Rod J. Rohrich, M.D., accompanies this article. Go to PRSJournal.com and click on "Plastic Surgery Hot Topics" in the "Videos" tab to watch. On the iPad, tap on the Hot Topics icon.

countries.[2] Years later, frameworks for understanding barriers to surgical care in low- and middle-income countries are still in development, as the Lancet Global Surgery 2030 Commission, spearheaded by plastic and reconstructive surgeons, launched a series of articles that investigated the growing need for surgical care in lower and middle income countries, along with successes and challenges of strategies to scale-up surgical services.[3] A common theme in these articles is a frustration with the dearth of rigorous data addressing access to surgical care in low- and middle-income countries. In this article, we present key findings of a large-scale initiative to understand barriers to plastic and reconstructive surgical care in Vietnam, a representative low- and middle-income country in Southeast Asia.

Existing models for barriers to health care often combine primary care (including preventative services) and surgical care, and fail to recognize the unique requisites of the latter (e.g., the need for specially equipped facilities, the demand for specialized physicians, and the high level of follow-up care for certain diseases). Surgical care must also be understood in relation to socioeconomic, cultural, and psychosocial elements. For these reasons, surgical care, and barriers to accessing it, must be analyzed and understood within a unique context. Unfortunately, few evidence-based studies have been conducted on barriers to surgical care in low- and middle-income countries; of those that have, the majority are specific to single-intervention procedures.

We investigated barriers to surgical care at medical missions in Vietnam sponsored by Operation Smile, a nonprofit organization dedicated to the repair of cleft lip and cleft palate for children around the world. Cleft lip and cleft palate represents the most common craniofacial congenital defect, with a birth prevalence of one in 500 to one in 2500 worldwide.[4] Not only does the defect result in physical obstacles to feeding and language development, but patients are often subjected to significant social stigma.

We present data from Vietnam for both single- and multiple-intervention cleft repair to introduce a comprehensive analysis of barriers to surgical care. Based on our evidence, in conjunction with the existing literature, we recommend a modified model to describe barriers to health care that addresses the particular needs of surgical patients and accounts for the complexities of surgical and postoperative care. This type of evidence-based framework for the structural and behavioral determinants of surgical care access is necessary to allow policymakers, donors, and other key stakeholders to develop policies and programs that effectively address barriers to obtaining surgical care.

In recent years, the academic community, and specifically the plastic surgery community, has raised its commitment to global surgery, reflected in recent publications that highlight international partnerships and well-designed evaluations of surgical delivery systems as key components to sustainable solutions.[3,5,6] Our study represents this growing commitment to higher level investigations in global surgery that can be used as a springboard for further study.

PATIENTS AND METHODS

In this cross-sectional study, surveys were administered to members of households who attended the Operation Smile International 25th Anniversary multisite missions in Vietnam in November of 2014. Eligibility criteria were individuals of any age currently residing in Vietnam with a cleft lip and/or cleft palate with or without previous surgical repair. Missions were completed in the cities of Hanoi, Nghe An, Hue, Ho Chi Minh City, An Giang, and Bac Lieu. Among 884 eligible patient households, 51 percent (453 households) were randomly surveyed. Depending on the number of households/patients at each site, every other or every third household/patient was approached for participation.

Through collaboration with the Vietnamese Fund for Children, local bilingual (English-Vietnamese) medical and dental students verbally administered the survey. All volunteers underwent an 8-hour training course led by study investigators to ensure consistent data collection, professionalism, and cultural sensitivity when surveying patients and families about their social/medical history and cleft disease. At each mission site, a study investigator oversaw surveyors and reviewed each survey for consistency and completeness.

As most orofacial cleft patients were children, surveys were administered in a confidential setting to a member of the household aged 17 years or older who was deemed an authority in the household and able to answer medical history and questions regarding familial decision processes (e.g., a parent, grandparent, aunt/uncle, or other family member/close friend).

A portion of households/patients had undergone cleft surgery previously and attended the current mission with the hope of undergoing surgery for a related defect or revision operation to improve their results. As such, the survey was

adapted into two versions: one for individuals who had had prior surgical repair of the cleft lip and/or palate and one for those who had no previous surgery.

Demographic and access/barriers to care questions were taken from the validated World Health Organization Survey of Health and Health System Responsiveness. Questions specific to medical and surgical history were adapted from a validated survey created for the International Family Study, an epigenetic cleft study designed by the University of Southern California during similar Operation Smile International missions.[7] Data analysis included descriptive statistics and comparisons between those who had undergone past cleft surgery versus those who had not (Stata 12.0; StataCorp, College Station, Texas).

RESULTS

A total of 884 households presented to the cleft missions sites and 453 were randomly surveyed. One hundred percent of approached households chose to participate in the survey. Table 1 shows demographic characteristics of household participants and stratified access to care data. The proportion of patients with cleft lip, cleft palate, or cleft lip and palate differed significantly by households who had received cleft surgery in the past compared with those that had not (23, 28, and 49 percent, respectively; $p < 0.001$). Overall, the mean age at the time of first cleft surgery was 3.24 years. Current patient age, patient age at the time of first surgery, and health insurance status differed significantly by surgical status. The mean age of patients who were undergoing surgery for the first time at the current mission was 2.61 years; for those who had undergone cleft surgery before the current mission, the mean age at the time of first surgery was 3.78 years ($p = 0.004$).

Median and mean annual income of each household at the mission was $1700 and $2390, respectively. Mean annual income per household member was $530. Most household adults were farmers by trade (53 percent of fathers and 52 percent of mothers), followed by unskilled labor workers and those who were self-employed. A majority of mothers and fathers had finished secondary (middle) school or higher (55 percent and 54 percent, respectively) (Table 2). Mothers and fathers were more likely to have finished secondary school for patients who were able to obtain previous surgery ($p = 0.05$ and $p = 0.0020$, respectively), and the mother's occupation was correlated with whether or not the child received cleft surgery in the past ($p = 0.02$).

Eighty-five percent of households who had not received surgery in the past reported having insurance, whereas only 63 percent of households who had surgery in the past reported having insurance ($p < 0.001$). Of those households/patients who had surgery previously, 83 percent had their surgery performed by a charity. Most households reported having a local hospital with surgical facilities that was more accessible than the mission site, but stated that they could not obtain surgical cleft treatment at these facilities largely because of the cost of care (Table 1).

Each household had an average of 4.8 members, with an average of one person per household able to see a primary care physician in the past 3 months. On average, one of four people per household needed to see a physician but did not or could not; one in five people per household saw a surgeon in the past 3 months, and one in seven persons who needed to see a surgeon did not or could not. If not given surgical care during the current mission, 43 percent reported that they did not have access to any other form of surgical cleft care. If not provided nonsurgical care for their cleft (e.g., general pediatric, dental, or speech therapy) at the current mission, 41 percent reported they did not have any other access to such care.

The impact of structural, financial, and cultural barriers is summarized in Figure 1. Structural barriers, such as the lack of trained medical personnel (66 percent) and lack of equipment/medicine (67 percent), were the most commonly reported obstacles to obtaining surgical cleft care for households/patients. Significant financial barriers to care included treatment costs (54 percent), lack of savings (57 percent), travel costs (60 percent), and food/living expenses necessary to travel for care (64 to 66 percent). With respect to cultural barriers, most households cited family opinion/permission (68 percent), lack of trust in the medical system/personnel (54 percent), and poor quality of available treatment (43 percent) as obstacles to obtaining surgical cleft care.

DISCUSSION

Several important findings emerged from this patient-centric study of access to plastic and reconstructive surgery. First, the total proportion of insurance coverage is high (73 percent) among these communities in Vietnam. Second, despite high rates of insurance coverage, households have considerable difficulty accessing surgical care, and the

Table 1. Demographic Characteristics and Barriers to Surgery for Households/Patients Surveyed

	No Previous Surgery (%)	Previous Surgery (%)	Total (%)	*p*
Diagnosis				
Cleft lip	69 (34)	31 (13)	100 (23)	
Cleft palate	79 (39)	45 (18)	124 (28)	<0.001*
Cleft lip and cleft palate	55 (27)	166 (69)	221 (49)	
Sex				
Male	124 (60)	107 (44)	260 (57)	0.197*
Female	83 (40)	136 (56)	190 (43)	
Age				
Patient age, yr	2.58	6.71	4.82	<0.001†
Patient age at time of first surgery, yr	2.61	3.78	3.24	0.004†
Annual income‡				
Household income	$2461	$2328	$2390	0.586†
Household income per person	$543	$518	$530	0.645†
Hospital access				
Closest hospital, hr	0.79	0.79	0.74	0.379†
Closest hospital, km	15.89	15.89	20.90	0.130†
Travel cost to closest hospital‡	$13.84	$15.73	$14.94	0.610†
Insurance				
No	24 (15)	72 (37)	96 (27)	<0.001*
Yes	132 (85)	124 (63)	256 (73)	
Reasons for not seeing a doctor				
Cost	30 (61)	35 (49)	65 (54)	
Too far	7 (14)	15 (21)	22 (18)	
No time	8 (16)	10 (14)	18 (15)	0.156*
Fear	2 (4)	4 (6)	6 (5)	
Other	2 (4)	8 (11)	10 (8)	
Reasons for not seeing a surgeon				
Cost	16 (39)	19 (56)	35 (47)	
Too far	8 (20)	8 (24)	16 (21)	
No time	7 (17)	6 (18)	13 (17)	
Fear	4 (10)	0 (0)	4 (5)	0.310*
Poor health	3 (7)	0 (0)	3 (4)	
Lacked information	2 (5)	0 (0)	2 (3)	
Family disagreed	1 (2)	1 (3)	2 (3)	
Travel cost to nearest facility				
0–99,999 VND ($0–$4.49 USD)	70 (49)	95 (48)	165 (48)	
100,000–199,999 VND ($4.50–$8.99 USD)	26 (18)	33 (17)	59 (17)	
200,000–299,999 VND ($9.00–$13.49 USD)	11 (8)	23 (12)	34 (10)	0.610†
300,000–399,999 VND ($13.50–$17.99 USD)	12 (8)	11 (6)	23 (7)	
400,000–499,999 VND ($18.00–$22.49)	4 (3)	2 (1)	6 (2)	
>500,000 VND (≥$22.50)	19 (13)	35 (18)	54 (16)	

*χ^2 test.
†*t* test.
‡U.S. dollars.

vast majority (>80 percent) still rely on charitable care outside of the centralized health care system. This discrepancy leads to creating a more surgically centered public health model for understanding barriers to surgical care, to better serve patients in low- and middle-income countries. Finally, as a result, surgical treatment of congenital conditions, such as cleft lip and palate, is delayed beyond the standard optimal window compared to more developed countries. Although reconstructive surgery experts agree that surgical repair of cleft lip and cleft palate should be performed between 3 and 18 months of age to optimize surgical results and ability to feed and phonate,[8] cleft individuals in our study underwent their first cleft repair operation at an average age of 3.24 years.

Several public health models have been developed to categorize and evaluate access to health care (summarized in Table 3). The most cited nonsurgical health care model is Andersen's Behavioral Model of Utilization. Several models are derived from Anderson's paradigm, but few specifically address surgical intervention.[9] Irfan et al. combined Phillips' adaptation of Andersen's model[10] with the World Health Organization health systems concept to create the Healthcare Barrier Model for both surgical and nonsurgical care.[9] This model deconstructs patient-level barriers into several variables (i.e., predisposing, enabling, and need-based) but does not clearly identify which factors are specific to surgical versus nonsurgical care. In a systematic review, Grimes et al. present the most commonly

Table 2. Socioeconomic Demographics of Household Parents

	Father			Mother		
	No Previous Surgery (%)	Previous Surgery (%)	*p*	No Previous Surgery (%)	Previous Surgery (%)	*p*
Occupation						
Farming	108 (52)	135 (54)		103 (49)	137 (55)	
Government/public employee	7 (3)	5 (2)		12 (5)	10 (4)	
Housewife/unemployed	3 (1)	1 (0)		31 (14)	25 (10)	
Labor worker (unskilled)	20 (9)	24 (9)		23 (11)	25 (10)	
Professional employee	8 (3)	7 (2)		9 (4)	3 (1)	
Self-employed	25 (12)	23 (9)	0.181*	18 (8)	27 (10)	0.018*
Service	19 (9)	14 (5)		6 (2)	1 (0)	
Labor worker (skilled)	3 (1)	7 (2)		2 (0)	4 (1)	
Military	2 (0)	1 (0)		0 (0)	0 (0)	
Other	5 (2)	19 (7)		1 (0)	9 (3)	
Omitted	7 (3)	10 (4)		2 (0)	5 (2)	
Education						
None	13 (6)	26 (10)		15 (7)	12 (4)	
Some primary school	16 (7)	17 (6)		16 (7)	21 (8)	
Completed primary school	44 (21)	78 (31)		53 (25)	86 (35)	
Completed secondary school	55 (26)	63 (25)	0.110*	55 (26)	66 (27)	0.102*
Completed high school	47 (22)	36 (14)		42 (20)	36 (14)	
Completed university	24 (11)	13 (5)		23 (11)	13 (5)	
Omitted	8 (3)	12 (4)		3 (1)	10 (4)	

*Chi-squared test.

cited model for barriers to surgical care using three broad categories: structural aspects, cultural beliefs and attitudes, and financial barriers.[11] The model proposed by Grimes et al., although compelling, was created based on short-term, single-intervention operations such as cataracts/glaucoma (ophthalmologic) and antenatal/delivery (obstetric). Although certain barriers apply to all types of surgery (e.g., anesthesia, fear), specific classes of surgical disease present different barriers at each level, both perceived and real.

Past models do not stratify medical or surgical care by the level of continuing care required. Although surgical repair for cleft lip may be a singular intervention, many cleft lip patients require several additional operations, such as scar revision, rhinoplasty, cleft palate repair, alveolar cleft repair, fistula repair, and others. Cleft palate patients require multiple revisions to improve speech over years of care and extensive postoperative rehabilitation through speech therapy. To this point, the majority (54 percent) of households in our random sample were returning to the mission for revision surgery and follow-up medical treatment or speech therapy. In addition, cleft patients are in need of comprehensive, long-term care that includes maxillofacial, dental, speech, hearing, and psychosocial aspects. Given the magnitude of care needed for cleft patients, cleft treatment needs and barriers may be best examined in the context of a "chronic" disease. Clefts and other surgical conditions that require multistage reconstruction or longer term follow-up must be addressed differently when creating a public health model to understand barriers to care. Although some elements of comprehensive care can be provided in a mission setting, cleft patients need comprehensive therapies long term, and these change with an aging child. This study primarily addressed access to initial cleft care; further work will need to examine whether different barriers affect later stages of comprehensive cleft care. Finally, certain disease states, such as cleft lip, are easily recognized by laypersons, which leads to stigmatization and community pressure for treatment. Patients requiring plastic surgical reconstruction often suffer from similar stigmatization (e.g., individuals with burns, craniofacial defects, limb defects, and large wounds). The perception or reality of external pressures to obtain treatment is separate from what Grimes et al.[11] and Irfan et al.[9] refer to as "acceptability," which is the cultural or social resistance to obtaining treatment.

A majority of past models are also limited in their capacity to address barriers specific to surgical care. In this study, the lack of qualified surgeons and lack of surgical equipment were the most frequently cited barriers to obtaining needed surgery. The most commonly cited cultural barrier to care was distrust of the medical system because of both corruption and suspicion of medical providers, which was heighted by the perceived invasiveness of surgery. In addition, barriers for multistage operations may exacerbate existing perceived provider-level limitations and patient factors.

The financial barriers identified in our population have been described in past models (i.e.,

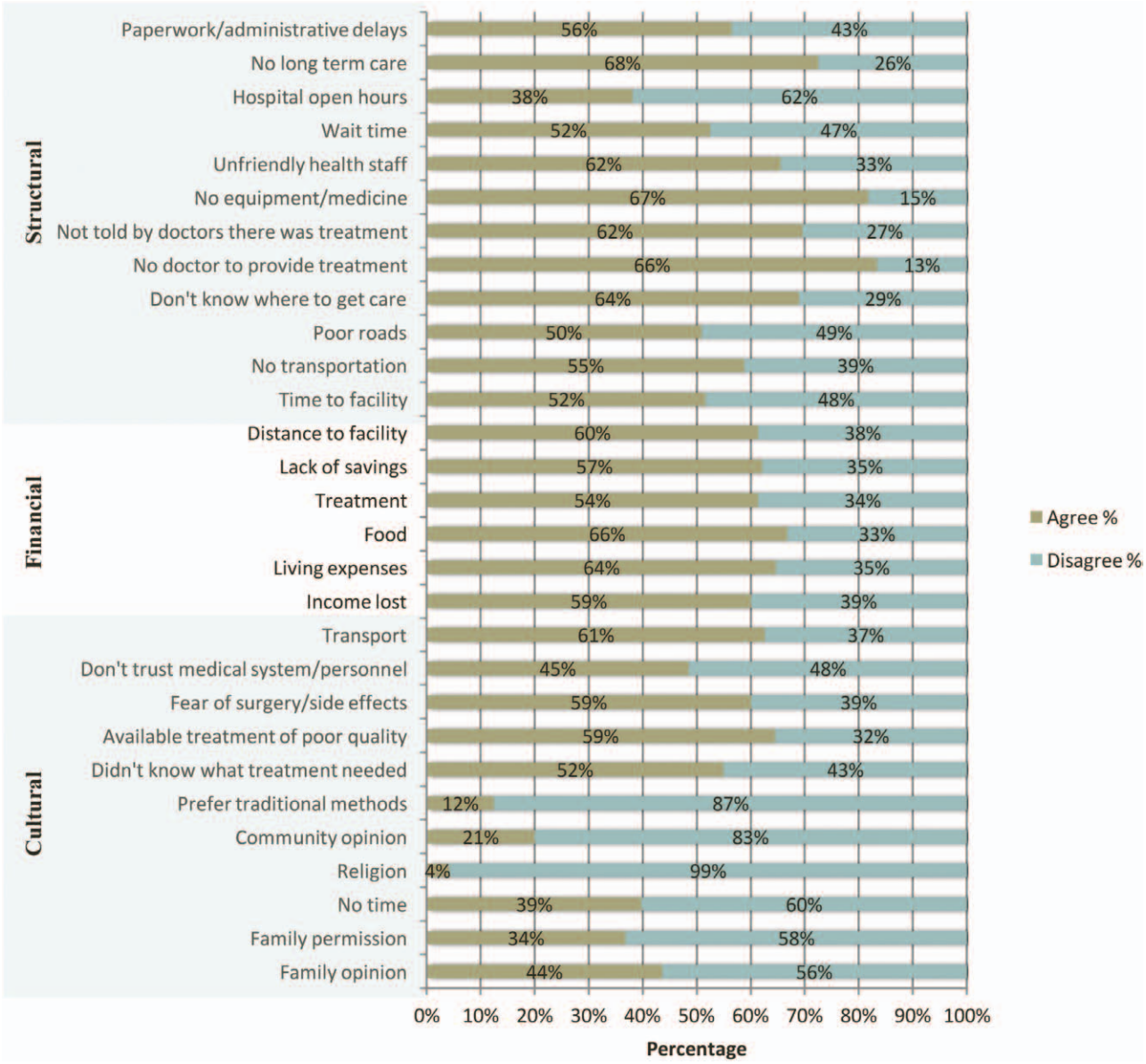

Fig. 1. Barriers to surgical cleft care as percentages of respondents/households.

treatment costs, lack of savings, and travel/living expenses). However, qualitative data from our study showed that the lack of accurate information and education in this population may have led to inflated perceptions of costs and a diminished perception of the benefits of surgical intervention. Although the model proposed by Grimes et al. subjugates "no perceived need" and "lack of understanding of severity of condition" as barriers related to cultural beliefs and attitudes,[11] it does not specifically address how a patient's perception of a health care problem and the corresponding solution pervasively affect care-seeking behavior. Similarly, Irfan et al.'s Healthcare Barrier Model mentions how perceptions, knowledge, and beliefs are barriers within patient-level factors[9] but does not describe or define what "perceptions" are; furthermore, they do not propose how and why perceptions impact the decision to obtain surgery. No previous models clearly delineate patient perceptions, which we define as a non–community-, culture- or religion-specific personal modifier that may change over time. As such, public policies aimed at medical information and cost transparency and health education are essential for the improvement of barriers to surgical care discussed in this article.

Our data highlight barriers specific to surgical care within the health systems context of a low- and middle-income country that are not addressed in previous research. Table 3 summarizes which

Table 3. Past and Proposed Barrier/Access to Health Care Frameworks*

	Environment	Structural	Health System	Provider	Culture	Patient Predisposing	Patient Perceptions	Nature of Disease
Nonsurgical disease								
Obrist	+	+	+	+	+	+	-	-
McIntyre	-	-	+	+	+	+	-	-
Anderson	+	+	+	+	-	+	-	-
Surgical disease								
Grimes	-	+	-	-	+	+	+	-
Health care barrier model	+	+	+	+	+	+	-	-
Surgical LMIC model (proposed herein)	+	+	+	+	+	+	+	+

LMIC, low- and middle-income country.
*Irfan FB, Irfan BB, Spiegel DA. Barriers to accessing surgical care in Pakistan: Healthcare barrier model and quantitative systematic review. *J Surg Res.* 2012;176:84–94; Phillips KA, Morrison KR, Andersen R, Aday L. Understanding the context of healthcare utilization: Assessing environmental and provider-related variables in the behavior model of utilization. *Health Serv Res.* 1998;33:571–596; Grimes CE, Bowman KG, Dodgion CM, Lavy CB. Systematic review of barriers to surgical care is to surgical care in low-income and middle-income countries. *World J Surg.* 2011;35:941–950; The World Bank. GDP per capita (current US$). Available at: http://data.worldbank.org/indicator/NY.GDP.PCAP.CD. Accessed March 10, 2013; McIntyre D, Thiede M, Birch S. Access as a policy-relevant concept in low- and middle-income countries. *Health Econ Policy Law* 2009;4:179–193.

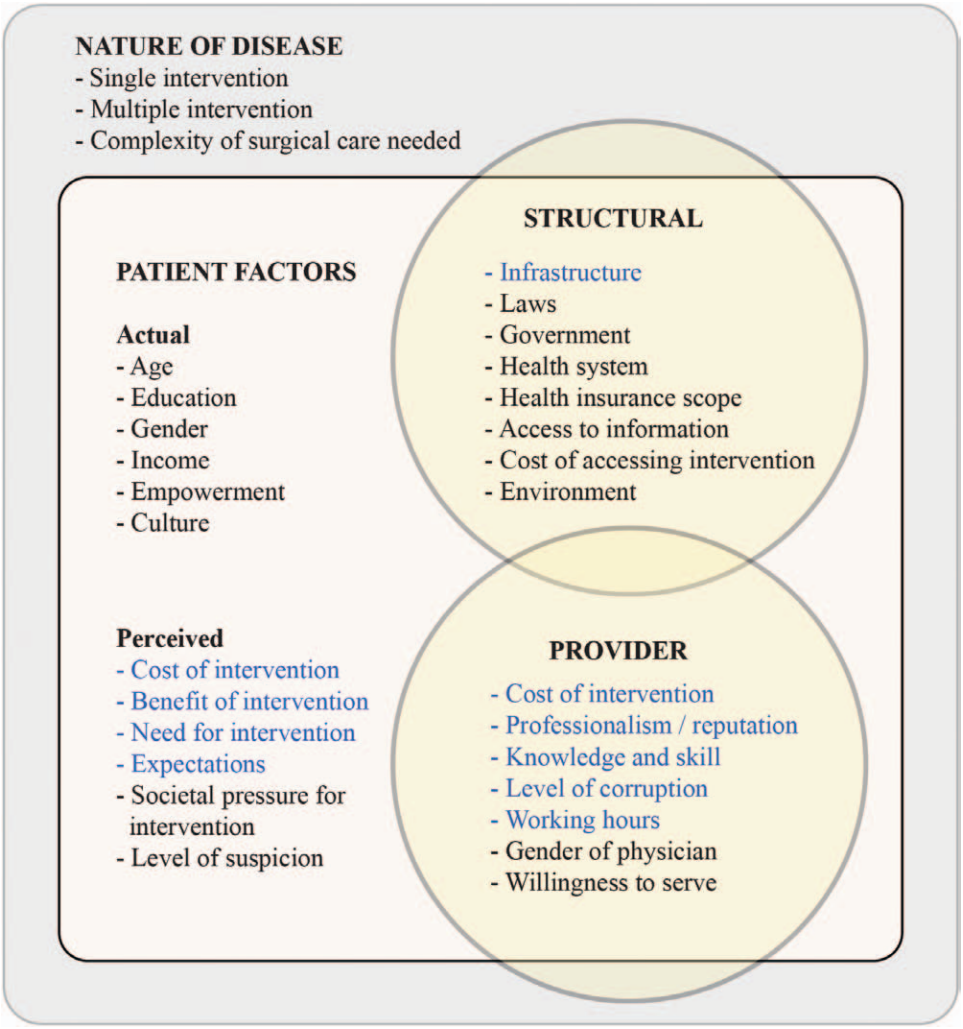

Fig. 2. Proposed barriers-to-care framework using the surgical low- and middle-income country model. Items in *blue* are factors that are particularly exacerbated by diseases that require multiple or a series of treatments/interventions.

factors are included in past models for barriers to care and highlights the elements that we propose to modify and/or introduce. Our proposed framework to organize barriers to surgical care, the "surgical low- and middle-income country model" (Fig. 2), augments current models by addressing three key elements: barriers specific to surgical care; single- versus multiple-intervention diseases; and specific low- and middle-income country challenges (e.g., perceived versus real barriers on a patient level). In Figure 2, items in blue are factors that are particularly exacerbated by diseases that require multiple or a series of treatments/interventions, which reconstructive surgery often requires.

The conclusions from this study and the proposed model developed as a result can be generalized for other populations in Vietnam and similar low- and middle-income countries. For Vietnam specifically, our study cohort provides a strong representation of the national population: households surveyed were comparable in income, occupation type, and education level to the nation's lower and middle class population; the reported annual household income for our study population was on par with Vietnam's gross national income per capita in 2013[12]; and the majority of our study population were farmers, parallel to national statistics that report 51 percent of adults being employed in the agricultural sector.[13]

As with most cross-sectional studies, the primary limitations of this study are the potential for selection bias and limited generalizability. Individuals were recruited from surgical missions where households were proactive in seeking care and had the time/means to spend several days at the mission site. Although Operation Smile reimbursed travel, food, and lodging fees, those at the mission likely represented a more economically secure and/or educated subset. Missions were announced on billboards, on television, on the radio, by community health workers, and by word of mouth; nevertheless, even these varied forms of messaging may not have reached the most marginalized people. In addition, our results may be specific to the local context of Vietnam, which may differ significantly in religious/spiritual, educational, cultural, and economic characteristics compared with other low- and middle-income countries. Although our model may be more generalizable to regional low- and middle-income countries elsewhere in Southeast Asia with similar political and structural infrastructure, it is worth noting that Vietnam's gross domestic product per capita is higher than that of Cambodia, Myanmar, and Laos but lower than that of Thailand.[14–16]

Our data help validate existing health care barrier models through quantitative methods and support the development of a more evidence- and needs-based public health framework designed to modify health behaviors and perceptions regarding surgical care. Our surgical low- and middle-income country model accounts for barriers specific to surgical care, plastic surgical care, and low- and middle-income countries that are not addressed in previous models, including disease type/nature (single- versus multiple-intervention surgical disease) and patient perceptions. Although our barriers-to-care model was created using a cleft lip and palate population, we believe this model may be useful to understand barriers for a variety of reconstructive surgical needs such as for hand, burn, and trauma injuries, among others. It also highlights the challenges and successes for mission-based care and the need to better understand surgical barriers to design more effective programs for both mission-based and locally sustainable surgical care. Plastic surgeons are uniquely positioned to lead the surgical community in addressing the need for improvements in global surgical access and care, given our history of mission-based work, access to multicultural patients, and dedication to education systems within global surgery. Better understanding patient barriers to reconstructive surgical care can guide plastic surgeons in being more attuned clinicians and more informed directors of surgical outreach initiatives.

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Cleft-Related Infanticide and Abandonment: A Systematic Review of the Academic and Lay Literature

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Abstract

Objective: We aimed to describe the scope of cleft-related infanticide and identify issues that might inform prevention strategies.

Design: Systematic reviews of both academic (eg, PubMed, EBSCOhost) and lay literature (eg, LexisNexis Academic, Google) databases were performed to identify all primary reports of cleft-related infanticide. All languages were included. Records before 1985 were excluded. Reference lists of all included reports were screened for potentially relevant records.

Main Outcome Measures: Country of origin and excerpts that pertained to the concepts surrounding cleft-related infanticide were extracted. Extracted excerpts were examined using a content analysis framework.

Results: Of the 1,151 records retrieved, 70 reports documented cleft-related infanticide from 27 countries. The largest number of reports was from China (14 reports; 48% of reports), followed by India (4; 14%) and Nigeria (4; 14%). However, 2 countries had 3 reports, 5 countries had 2 reports, and 17 countries had 1 report. Themes that emerged from excerpt analysis included stigma, lack of affordable cleft care, abandonment, orphanage overcrowding, and abuse and slavery.

Conclusions: Cleft-related infanticide is a global problem. Initiatives to sensitize communities to cleft lip and/or cleft palate, provide timely and affordable cleft care, and build support systems for affected families may prove beneficial. Cleft care organizations have the opportunity to advocate for these initiatives, reduce the incidence of infanticide by providing or supporting timely and affordable cleft care, and demonstrate that children with successful cleft repairs reassimilate well into their communities.

Keywords

cleft lip and palate, infanticide, abandonment, human rights

Introduction

Cleft lip and/or cleft palate (CL/P) affects approximately 1 of every 600 newborns globally (Mossey et al., 2009). Thus, an infant is born with an oral cleft every 150 seconds, totaling more than 210,000 children per year (WHO, 2002). Fortunately, children who receive timely cleft care rarely die or suffer lasting disability as a result of their oral cleft (Carlson et al., 2015). However, access to timely cleft care varies considerably worldwide, resulting in disparate rates of death and disability between children in high-income and low- and middle-income countries (LMICs) (Mossey et al., 2009; Higashi et al., 2015).

To date, most cleft-related infant mortality estimates have relied on clinical and birth defect registries (Hujoel et al., 1992; Carlson et al., 2013; Cubitt et al., 2014; van Nunen et al., 2014). Such registries are lacking in many LMICs (Cubitt et al., 2014; Higashi et al., 2015); thus, mortality rate estimates are few, which range from 3.4% to 18% (Carlson et al., 2013). Further, clinical surveillance likely underestimates the actual mortality rate as it does not capture the deaths of children with oral clefts who did not seek care, who died before reaching care, or who were killed (Groen, Samai, Petroze, et al., 2012). The

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frequency of the latter, cleft-related infanticide, is unknown. However, in certain countries and communities, it may contribute significantly to the cleft-related mortality rate. Given infanticide is a preventable cause of mortality in this group, highlighting its existence and the issues that surround it may inform prevention strategies that avert needless deaths.

To give perspective to this problem, we aimed to systematically search both the academic and lay literature to find reports of cleft-related infanticide and describe the issues that surround it. By doing so, we might identify the potential for a significant, hidden cause of mortality among children with an oral cleft. In addition, the findings might add to the evidence base useful for advocating for better access to affordable cleft care, community cleft education, and support services for the families of children with an oral cleft.

Methods

A systematic review of both academic and lay literature databases was performed to identify primary reports of infanticide of a child or children with an oral cleft. The literature search and reporting for this systematic review was performed in accordance with the PRISMA guidelines (Moher et al., 2009).

Search Strategy

Terms for cleft lip and cleft palate and terms related to infanticide (eg infanticide, kill, die, died, murder) were used. PubMed, LexisNexis Academic, EBSCOhost, and Google were searched using database-specific language that included the aforementioned terms (eg, Cleft AND (Infanticide OR Kill OR Murder OR Die OR Died); ("Cleft Lip"[Mesh] OR "Cleft Palate"[Mesh]) AND "Infanticide"[Mesh]). LexisNexis Academic is a database that includes reports from many sources, including the global lay literature (eg, newspapers, magazines, blogs, wire services, broadcast transcripts) and law reviews. EBSCOhost catalogs academic records from a variety of disciplines, including psychology, anthropology, social work, development, criminal justice, family studies, humanities, and social science. Google was searched to capture recent records, particularly those in the lay literature that were yet to be cataloged by LexisNexis Academic. Given the purposefully overinclusive nature of Google search results, records were sorted by relevance and screening was terminated after 100 consecutive nonrelevant records. To eliminate remote reports of infanticide, only those that documented a case after 1985 were included.

Record Management

Retrieved records were compiled into a single database and duplicates were removed. After, records were screened for relevance. Titles and abstracts of records in non-English language were translated and screened for inclusion. No full-text report required translation. Full-text reports of relevant records were reviewed. The reference list from each full-text report, if present, was reviewed for potentially useful records. Reports were included if they were primary accounts of infanticide of a child(ren) with an oral cleft. If there was more than one report of the same infanticide event, only one report was included. From each report, the country and excerpts pertinent to the concepts surrounding cleft-related infanticide were extracted.

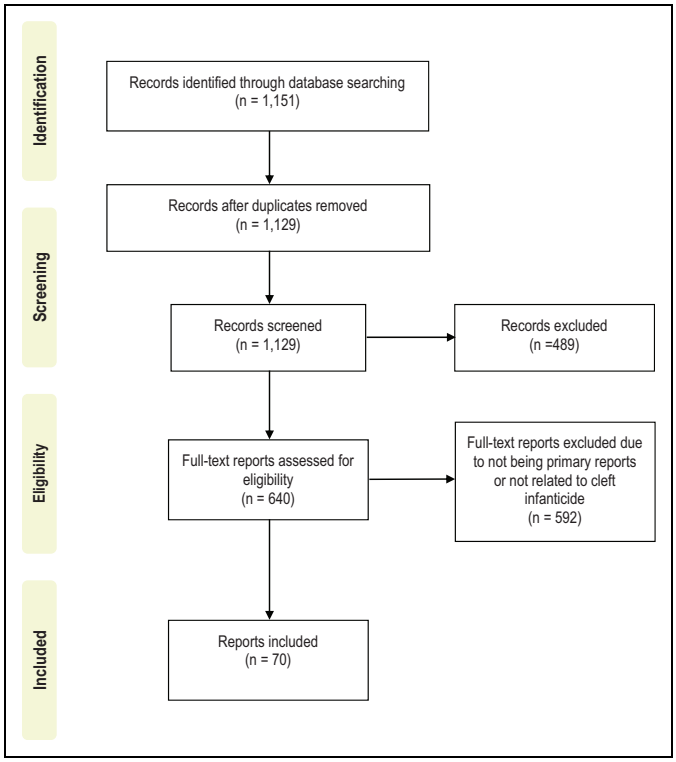

Figure 1. Flow diagram of results from systematic search.

Data Analysis

In addition to describing the reports, extracted excerpts were examined using a content analysis framework (Gale et al., 2013). First, excerpts were grouped into categories based on codes that represented clustered concepts. After, categories were further refined into useful themes, described, and are presented alongside representative quotations extracted from illustrative reports. Proper names were left out of the quotations and replaced with the appropriate noun in brackets (eg, "Jane" replaced with [mother]). Similarly, if a quotation referred to a person or situation that was described outside of the scope of the quote, text was added to provide context. All edited text is presented within brackets.

Results

Search Results

In total, 1151 records were retrieved by the search strategy (Figure 1). After duplicates and irrelevant reports were removed, 640 full-text reports were reviewed. Of these, 70 reports documented a cleft-related infanticide.

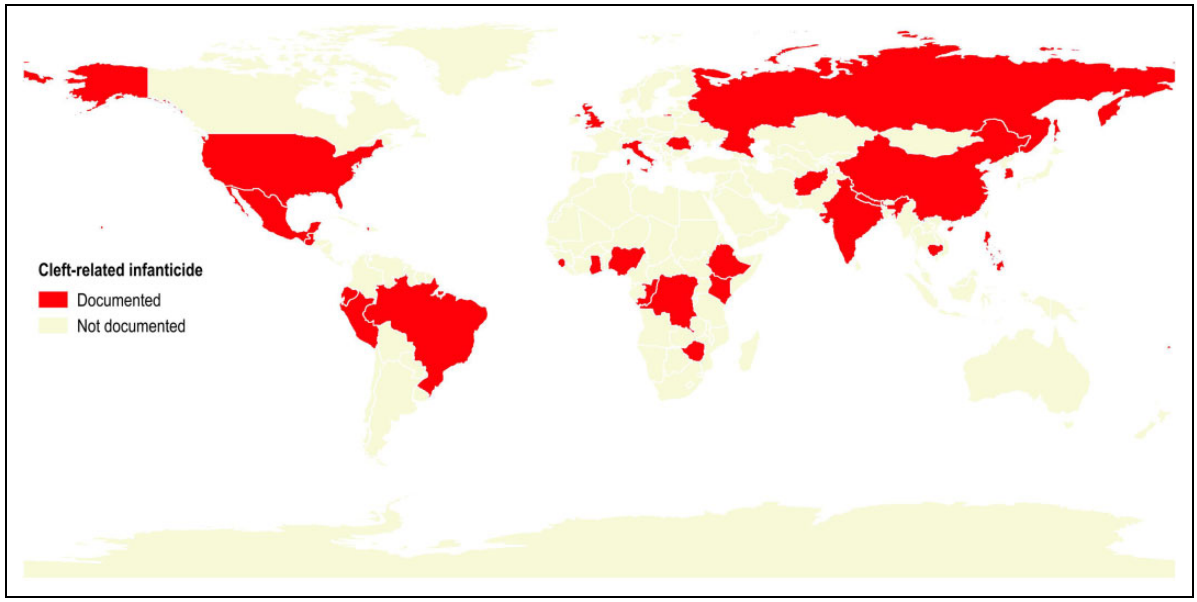

Figure 2. Map of countries with a documented case of cleft-related infanticide since 1985. Countries with documented cleft-related infanticide include Afghanistan, Brazil, Cambodia, China, Republic of the Congo, Democratic Republic of the Congo, Ecuador, Ethiopia, Fiji, Ghana, United Kingdom, Guatemala, Haiti, India, Italy, Kenya, Mexico, Nepal, Nigeria, Peru, Philippines, Romania, Russia, Sierra Leone, South Korea, The United States of America, and Zimbabwe.

Cleft-related infanticide was documented in 27 countries (Figure 2). The largest number of reports were from China (14 reports; 48% of reports), followed by India (4; 14%), Nigeria (4; 14%), Russia (3; 10%), and Peru (3; 10%). However, 5 countries had 2 reports and 17 countries had 1 report.

Several themes emerged from analysis of report excerpts pertinent to the concept of cleft-related infanticide. The themes included stigma, lack of affordable cleft care, abandonment, orphanage overcrowding, and abuse and slavery. Examples of each of these are potentially instructive.

Stigma and Being Cursed

Reports repeatedly documented examples of the stigma that children with an oral cleft and their families face. Reports documented that the effects of the stigma are often transferred directly onto the parents, which was suggested to be a factor that contributed to abandonment and infanticide.

> [Children with an oral cleft] are subjected to bad mistreatment. It's seen as a stigma and they're excluded from communities, even to the point where their parents disown them.
>
> It's quite hard for them to be understood, so teachers refuse to teach them. Sometimes parents just leave them to die.
>
> In Peru, being born with a cleft lip or palate means shame is part of your birthright. Other children don't play with you. Your parents hide you or kill you. If they don't, they risk their jobs to keep you around. You are a modern-day leper.

Reports also described parents, families, and communities that believed that children with an oral cleft were cursed or might curse the community. Reports implied that abandonment or infanticide in this group was punishment for the child or perceived as a way to protect the family and/or the community.

> [Children with an oral cleft] are thought to cause life-threatening fright sickness.
>
> I have experienced all sorts of abuses and rejection from my husband's family [due to having a girl with a cleft lip]. They believed that the child was evil. Some people instructed my husband to force me to stop feeding the baby at birth, so that she could die.
>
> [The community] sees cleft children as bad omens to the family or even witches. Some children born with cleft are either dumped in a river or [an] unused well to die or denied food and allowed to die slowly.
>
> [There was] a couple that had twin children [with oral clefts] and we fixed them. Instead of the man [being] happy, he cried like a baby. We said, "You should be happy." He said, "No." [His] first child had a cleft and he did not know what to do with it. [The community] said he had brought calamity to them. He threw the child into the river.
>
> Babies who are born "different" are labeled *kinkirgo*—"spirit children." They are considered semi-human, and are believed to be possessed by dark forces, and therefore bringers of bad luck. In most societies, killing a child is murder, but in this part of Ghana it can be arranged legally and costs four fowls and a goat. The killer—the "concoction man"—is treated like a guru, both revered and feared.

Lack of Affordable Care

Most of the included reports described or eluded to situations where timely, affordable cleft care was not available. The reports suggested that the financial and emotional burdens

placed on the family to care for a child with an unrepaired oral cleft, particularly when there was no hope of repair, contributed to abandonment and infanticide.

> In early June, a family of four were tried in a court in Zhejiang Province for abandoning their baby, which was born with a cleft lip and palate. The family claimed that they were too poor to afford the surgeries to treat the condition.
>
> After her parents, who are both migrant workers in Guangzhou, Guangdong Province, had spent all of their savings on medical treatment for the baby [with a cleft palate], the father decided he should leave his new-born daughter in the Guangzhou "baby hatch"—a controversial facility in which parents can leave children to be found by welfare centers. However, days later, policemen found Chen and arrested him because the infant was found to have died [before she was found by welfare center caregivers].
>
> He knew his daughter probably wouldn't survive if she stayed in Guatemala. Medical personnel there advised him to let her die.
>
> [A girl] had been born [with a cleft lip and palate] and doctors put her in a broom cupboard to await transfer to an institution the next day. [Her mother] had been told by the authorities that nothing could be done.

Abandonment

A number of reports documented the abandonment of a child with an oral cleft. The reports are unclear and varied with regard to the usual intent of abandonment (ie, giving the child to an orphanage or other organization to care for the child vs leaving the child to die).

> Earlier this week, another newborn with a cleft lip was left by her parents outside a garment factory in Phnom Penh. Workers found the days-old infant covered in ants and starving and took her to the hospital.
>
> At any rate, it is a common reason for abandoning a child at birth. Children with cleft palates are invariably labeled as mentally subnormal.
>
> For many of the forty boys and girls, the lying room is the final stop before burial in an unmarked grave. Their parents abandoned them rather than face the stigma of bringing up an "imperfect" child in a society that abhors disability.

Orphanage Overcrowding

Abandoned children who are found alive often end up in an orphanage. Reports documented substandard care at orphanages, mainly due to the large numbers of children with special needs they are expected to care for with inadequate numbers of staff and resources.

> Children [with special needs, including those with an oral cleft] were tethered like dumb animals. Toddlers were secured to bamboo seats with their legs splayed over makeshift potties. Children were tied four in a row, rocking mindlessly back and forth.
>
> It is not unusual for infants [with special needs, including those with an oral cleft] to die of malnutrition with full bottles at their sides, thrown into cribs by workers too busy to feed them.
>
> [Some] deaths at the [orphanage] were the result of a "sinister" and "apparently systematic program of child elimination in which senior medical staff played a central role."

Abuse and Slavery

Some reports documented abuse and/or slavery of children with an oral cleft.

> Abused by her family who mistreated her terribly, she was left to sleep outside in a cardboard box and then sold to a man who went on to abuse her.
>
> [Cleft lip repair] surgery wasn't available at the local hospital. There was a remote possibility that the Red Cross would fly a surgeon in or the boy [with a cleft lip] could be referred to the free hospital in Kabul. The problem with the latter was that it wasn't really free at all. A backhander would be required for the surgeon; but as [the child's] family were subsistence dwellers, they had nothing to give.
>
> It was put to me that they could give away their youngest daughter, quite likely to a life as an unpaid domestic helper.

Discussion

This study aimed to give perspective to the problem of cleft-related infanticide and provide evidence that might be used when advocating for greater cleft care capacity, community cleft education, and social support services. Although the findings from retrieved reports demonstrated that cleft-related infanticide continues to occur and happens globally, there is an extreme dearth of data on this issue. Any child with an oral cleft who is born in a community where clefts carry significant stigma or in a community without access to cleft care, social support services, or child legal protection is particularly vulnerable to infanticide and abandonment. To address this issue, we must consider the motives for infanticide and develop ways to mitigate them.

While infanticide of children with disabilities has been practiced since the beginning of civilization, the incidence of its practice in contemporary societies has not been well documented, particularly with regard to cleft-related infanticide (Porter and Gavin, 2010). The incidence of all-cause infanticide is underreported, but thought to be high in some societies (Pinheiro, 2006; Pitt and Bale, 1995). For example, a study of 1000 neonatal deaths in India found that 41% were due to infanticide (Pinheiro, 2006). Further, abnormal sex ratios among children in many countries and communities suggest that infanticide is more common than appreciated (Hesketh and Xing 2006). Globally, children with disabilities, including unrepaired oral clefts, are at highest risk of tacit or open abuse and infanticide (Pinheiro, 2006; Hibbard et al., 2007). A study of the association between child language disability, which is common in children with an oral cleft, and caregiver violence demonstrated that a child with a language disability received 26% more severe physical violence and/or corporal punishment than children without a disability (Hendricks et al., 2014). However, cleft-specific abuse and infanticide risk remains

poorly described. Although compounded by a high background neonatal mortality rate and genetic heterogeneity, the relatively low prevalence of oral cleft in some African communities and among females in Asia have raised concerns of cleft-related infanticide (Zeng et al., 1992; Butali et al., 2014). Given the risks aforementioned and the findings presented by the reports above, cleft-related infanticide is likely practiced commonly and requires dedicated efforts to eliminate the factors that are contributing to it.

To address cleft-related infanticide, the motives of the perpetrators must be understood. The well-described infanticide motive categories are (1) an unwanted child, (2) perceived altruistic or mercy killing, (3) stimulus rising outside of the victim, (4) stimulus rising from the victim, and (5) aggression attributable to mental illness (Pitt and Bale, 1995). Each of the five described categories of infanticide motives were present in the retrieved reports First, many women worldwide do not have access to family planning services and/or have limited sexual rights (Glasier et al., 2006; Emina et al., 2014). Thus, children are often born to women that are not ready or equipped to care for them (Wado et al., 2014). The addition of an oral cleft to this already stressful situation may increase the risk of infanticide. Second, as evidenced by the excerpts above, some cases of infanticide are the result of parents that believed that they were protecting a child with an oral cleft and/or the family by killing them, thereby preventing them from experiencing a lifetime of shame and/or sparing other family members from shame. Similarly, the belief that a child with an oral cleft is cursed in some communities places undue pressure on parents to kill their child. External pressure is particularly evident in reports from China where parents are additionally subjected to the one-child policy (Hesketh and Zhu, 1997; Gillan, 2002). Women who are socially punished for having a child, whether through poverty, law, or stigma, may more often react in ways that harm their babies (Judy, 2002). Next, the expenses and emotional burden of caring for a child with an oral cleft, particularly for poor families, are other significant stressors that may contribute to abandonment or infanticide. Lastly, postpartum depression is an often-overlooked factor that frequently goes undiagnosed and untreated in many settings, particularly in LMICs (Kathree et al., 2014). These motives may work synergistically to increase the risk of cleft-related infanticide, making it difficult to address the issue from a single discipline.

Although cleft-related infanticide should not be beyond reproach of the law, it is often the result of strong cultural pressures and beliefs, as well as a lack of affordable cleft care, social support systems, and postpartum care. Thus, each of these factors must be addressed to prevent infanticide. Cultural pressure, particularly with regard to social stigma and misguided beliefs about witchcraft, can be overcome by community cleft education (Naram et al., 2013). Many examples of successful community sensitization of a previously stigmatized condition exist, such as for HIV and mental illness (Stangl et al., 2013; Griffiths et al., 2014). However, congenital anomalies are rarely included in community health or perinatal education initiatives (Chan et al., 2006; Naram et al., 2013). Thus, examples of successful community health education initiatives could be used as models for programs aimed at improving the knowledge of the causes, treatment options, and expected outcomes for oral clefts. The lack of timely access to affordable cleft care has been well documented, particularly in LMICs (Chirdan et al., 2010; Adetayo et al., 2012; Groen, Samai, Stewart, et al., 2012; Carlson et al., 2015; Mock et al., 2015; Nagarajan et al., 2015). Improving the capacity for cleft care, including surgical services, will require a sustained commitment and investment by national governments and international partners (Mock, 2013; Mock et al., 2015; Stewart et al., 2015). However, cleft care organizations can significantly reduce the burden of unmet cleft need in the meantime and mitigate this added pressure on parents by providing cleft care to those without access (Carlson et al., 2015). Further, children who receive successful treatment and reassimilate into their communities can serve as ambassadors and potentially reduce stigma within their communities. The financial and emotional burden of caring for a child with special needs can be enormous, particularly on families already strained by poverty (Pinheiro, 2006; Hibbard et al., 2007; Hendricks et al., 2014). Thus, the potential impact of government and nongovernmental organizations that support families with a child with special needs may be significant (Kuhlthau et al., 2005; Nidey et al., 2016). Lastly, healthcare systems might adopt active postpartum care initiatives to ensure that affected women, who may be withdrawn and not seek care, find the care that they and their child with an oral cleft require (Porter and Gavin, 2010). Although each of these initiatives might have an impact on cleft-related infanticide, the greatest effect will likely occur when they are taken up together, rather than individually.

Children with oral clefts that are abandoned and survive are often placed in the care of orphanages (Gillan, 2002). As evidenced in retrieved reports, some of the orphanages are considerably underresourced to care for the number and types of children they receive. Thus, child protection agencies should ensure that orphanages meet standards commiserate with local expectations. Additionally, children with oral clefts residing in them should be identified and referred for cleft care. Orphanages might be rewarding targets for cleft care organization missions. By treating a child with an oral cleft, they ultimately require less care and might be more likely to be adopted, in addition to experiencing an improved quality of life (Hansson et al., 2012).

Given the dearth of data regarding cleft-related infanticide, there need to be data collection systems to improve our understanding of the epidemiology and outcomes of children with oral clefts globally, as well as children with birth defects more broadly (Mossey and Modell, 2012). Such systems might include more detailed birth registries that include children who were born at home, be integrated with facility-based birth defect and child health surveillance systems, and be incorporated into national life table data capture mechanisms. By doing so, health, child protection, and legal systems might be able to target context-specific interventions aimed to prevent cleft-related infanticide and other poor outcomes more effectively.

While this study is the first to systematically document reports of cleft-related infanticide, several limitations are worth mention prior to interpretation of the findings. Infanticide is typically hidden and does not get reported (Pinheiro, 2006); this was demonstrated by the lack of reports and useful data regarding cleft-related infanticide. Further, communities that practice infanticide may be less likely to have a local media outlet or more likely to be heavily censored. Therefore, the results of our search unequivocally reflect substantial publication bias and likely represent only the tip of the iceberg of cleft-related infanticide and abandonment. An excerpt from a more in-depth report retrieved by our search highlighted this: "Tens of thousands of Chinese babies, perhaps 100,000 or more, are discarded annually. Disability is the largest category [of reasons for a child being discarded]: the range in the [orphanage] is depressingly predictable—lots of cleft [lips and palates], a few misshapen limbs, a lovely girl with almost no nose, an albino boy, deaf and blind children, and those with cerebral palsy" (Gittings, 2001). Similarly, descriptions of cases in some reports suggest that infanticide and abandonment is common by using words like "another newborn," "not unusual," "common reason for abandoning a child," as well as by describing established systems for abandonment and/or infanticide, such as "baby hatches" and "concoction men." The best alternative to the methodology we used for assessing the incidence of infanticide would be a community-based survey. However, social response bias, prohibitive study costs, and limited geographic range would have produced different, but potentially equally biased, findings. To avoid controversy, reports that described late-term or partial-birth abortions as a result of an in utero diagnosis of a cleft-lip and/or palate were not included. However, a number of reports and law reviews documented that this is not an uncommon practice in a number of high-income countries that have routine prenatal screening capacity (Morrison and Gillett, 2014). Despite these limitations, findings from this report allow reasonable conclusions to be drawn about the continued practice of cleft-related infanticide and factors that may contribute to it.

Conclusion

Cleft-related infanticide continues to be practiced worldwide, and may be particularly common in China and India. Perhaps the most significant factors that contribute to cleft-related infanticide include overwhelming social stigma and lack of timely, affordable cleft care. However, insufficient social support systems and postpartum care likely contribute as well. If abandoned infants survive, they often are placed in overcrowded orphanages with inadequate resources to care for children with special needs or are abused or sold. To address this problem, parallel initiatives aimed at sensitizing communities to oral clefts, providing timely and affordable cleft care, building social and financial support systems for affected poor families, and improving postpartum care may prove beneficial and potentially reduce the risk of cleft-related infanticide. Additionally, child protection agencies should ensure that orphanages meet local standards and that children with oral clefts residing in them receive cleft care. In the meantime, cleft care organizations have the opportunity to advocate for these initiatives, reduce the incidence of infanticide by providing cleft care, and demonstrate that children with successful cleft repairs can easily reassimilate into their communities.

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A Health Systems Perspective on the Mission Model for Cleft Lip and Palate Surgery: A Matter of Sustainability or Responsibility?

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Abstract: One in 700 children around the world are born with cleft lip and/or palate (CL/P). Although reconstructive surgery is widely available in high-income settings, over 2 billion people in low- and middle-income countries lack access to essential surgical care. The mission model has been demonstrated to be highly effective in responding to the global surgical workforce crisis, but has been questioned in regard to its sustainability, value, and overall impact. Through effective health systems integration, the mission model presents abundant opportunities for streamlined delivery and horizontal impact. Still, the primary goal of the mission model is direct care delivery; and although the value of sustainability is indisputably vital, we contend that the mission model, when executed responsibly, creates high-value, sustained impact on the individual lives of those presently in need. We furthermore advocate for the sustained commitment of implementing organizations, patient safety, local integration, and a new focus on patient centeredness as key elements of the responsible mission model.

Key Words: Care delivery value chain, Cleft lip and palate, global surgical workforce crisis, responsible mission model

(*J Craniofac Surg* 2015;26: 1079–1083)

One in 700 children around the world are born with cleft lip (CL) and/or palate (P).[1] In high-income countries, such as the United States or United Kingdom, reconstructive surgery is typically performed by the age of 2 years; yet in low- and middle-income countries (LMICs) over 2 billion people lack access to basic surgical services and billions more are unable to access surgery that is safe, timely, and effective.[2–4]

Since 1982, Operation Smile has conducted surgical missions in more than 50 countries around the globe to ensure free access to CL/P surgery for those in the greatest need.[5] During surgical missions, medical teams, comprised of a mix of local, regional, and international volunteers, conduct patient screening and provide reconstructive surgery for CL/P over a period of approximately 2 weeks. Over the past 32 years, Operation Smile has provided free life-changing surgery to over 200,000 people in LMICs across the globe.

As the global health community has shifted its focus to health systems strengthening, the mission model has been questioned as being ostensibly unsustainable and having the potential to distort local health systems.[6–8] Using a health systems-based perspective, we explore these questions and specifically the sustainability, value, and impact of the mission model. Additionally, we frame and discuss key considerations for responsibly implementing the mission model in low-resource settings, applying our 30-year institutional experience.

RESPONDING TO THE GLOBAL SURGICAL WORKFORCE CRISIS

Global surgery is a nascent but rapidly developing field. Initial efforts to assess surgical capacity in LMICs have shown severe shortages of resources across the board, but particularly in regard to human resources.[9] We are in the midst of a global health care worker crisis, and the lack of adequately trained surgical and anesthesia providers has been deemed the rate-limiting step in scaling up surgery in LMICs.[10,11] Although plastic surgery expertise is available in populous countries, such as China or India, there are less than one tenth of the potential providers per capita as in North America.[12] This issue is even more complicated for countries in sub-Saharan Africa (SSA), such as Uganda, which has 3 plastic surgeons for a population of 27 million.[12] In Zambia, for example, nearly 1000 children are born with CL/P each year, and there is only 1 plastic surgeon actively operating in the entire country.[12,13]

Two primary techniques have been classically used by national health ministries and international nongovernmental organizations (NGOs) to respond to the surgical workforce shortage in LMICs: (1) expanding training opportunities for providers; and (2) temporarily expanding the workforce with foreign providers (ie, the mission model).[9,14] Each of these models has their own unique advantages, and each should be viewed as complementary rather than competing. Expanding training opportunities is a fundamental prerequisite for increasing surgical capacity in low-resource settings. This can be achieved by increasing the number of surgery and anesthesia residency positions within a country, providing additional postgraduate medical education programs, or training physician extenders in a variety of task-shifting-style programs.[14–16] Each of these training systems possesses substantial potential and should be given high priority.

Still, training surgical providers takes time and overlooks those affected by CL/P at the present moment. Studies have shown that infants born with CL/P have significantly elevated risks of dying in the first year of life compared to unaffected individuals.[17] One study from China found that infants with isolated CL/P had nearly 7 times the risk of dying in the first month of life compared to the general population.[18] Cleft lip and/or palate directly increases pediatric risks

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of malnutrition and infection, 2 of the largest sources of under 5 mortalities.[17,19] It has been further suggested that the incidence of cleft palate in SSA has been substantially underestimated because many of these infants die before ever reaching health services.[20] Comprehensive cleft care has the potential to substantially reduce these risks, a central component of which is early operative intervention. Early palatoplasty in particular has been suggested as a key intervention for reducing mortality rates in children with CL/P in SSA.[20]

Although expanded training opportunities and capacity improvement must be accomplished for long-run development, there are major ethical implications entailed in overlooking present needs in favor of long-term gains. Access to surgery is an essential part of primary health care and a basic human right; and to reach these children affected by CL/P at the present moment, programs that directly expand surgical capacity and deliver care are critical.[21] The mission model has been developed and continues to be used to respond precisely to this call.

MISSION IMPACT AND SUSTAINABILITY

Sustainable development is fundamental for strengthening health systems in LMICs. Sustainable programming promotes locally driven impact that, at least theoretically, creates long-term solutions. Still, sustainability should not be considered a prerequisite for all global health programming.[22] During initial disaster response, for example, generating immediate results must, in principle, outweigh the issue of long-term sustainability.[23] Similarly, CL/P reconstructive surgical missions are able to affect immediate change with or without long-term capacity improvements.[5,23] Sustainable development is not the primary goal of the mission model. Rather, the goal is to achieve a sustained impact on individual lives. The mission model's primary goal is care delivery. This delivery model has been demonstrated to be immensely effective in accomplishing this objective.[5,7,23] It has furthermore been shown to be highly cost-effective, at a rate of between $32 and $104 per disability-adjusted life year averted.[23–25]

Sustainable elements, such as training local providers, engaging with Ministries of Health and advocating for safe surgery, are all important priorities, and Operation Smile incorporates these approaches into each of the individual country strategies.[4] The medical mission, however, remains relevant as a standalone program because it addresses the common denominator of the environments where Operation Smile works: a critical gap in access to surgical care. Missions are executed through a redistribution of global health resources or, stated another way, through the movement of resources, both human and material, from areas of abundance to areas of scarcity. Questions related to the sustainability of this model are often raised.[7,26] The assumption that the temporary import of capacity through a mission could be transformed into an organic self-propelling activity is unrealistic.[22] Instead, the authors believe that the question of sustainability should be examined from the perspective of the respective patient community and the implementing organization. In our view, the sustainability of medical missions has less dependence on the resource-constrained host environment and, instead, relies on the sustained commitment of the implementing organization.

Although the primary goal of CL/P surgical mission is care delivery, public health interventions often cause ripples in a health system, affecting the greater whole in an array of indirect ways.[27,28] Traditional public health thinking portrays health programs as unidirectional and 1-dimensional, distinguishing vertical or disease-specific programs from horizontal or system-wide programs.[28,29] This thought process, however, fails to recognize that all programs have horizontal and vertical dimensions and exhibit multilateral effects that can be acknowledged and capitalized upon.[27] These effects occur at the patient level, the provider level, and the system level.

The care delivery value chain is a tool developed by Kim and colleagues[27] to assist global health researchers in recognizing and developing these far-reaching effects. Experience and anecdotal evidence point to a broad range of downstream, "spill-over" effects secondary to surgical missions.[28] As shown in the literature and from the authors' collective experience, mission activities have led to the detection of primary heart defects, enrollment of malnourished infants into feeding programs, and informal yet effective training related to surgical technique, nursing care, speech therapy, and so on.[5,8,30,31] These benefits typically go unrecognized by traditional monitoring and evaluation techniques, though. In Figure 1, we use the

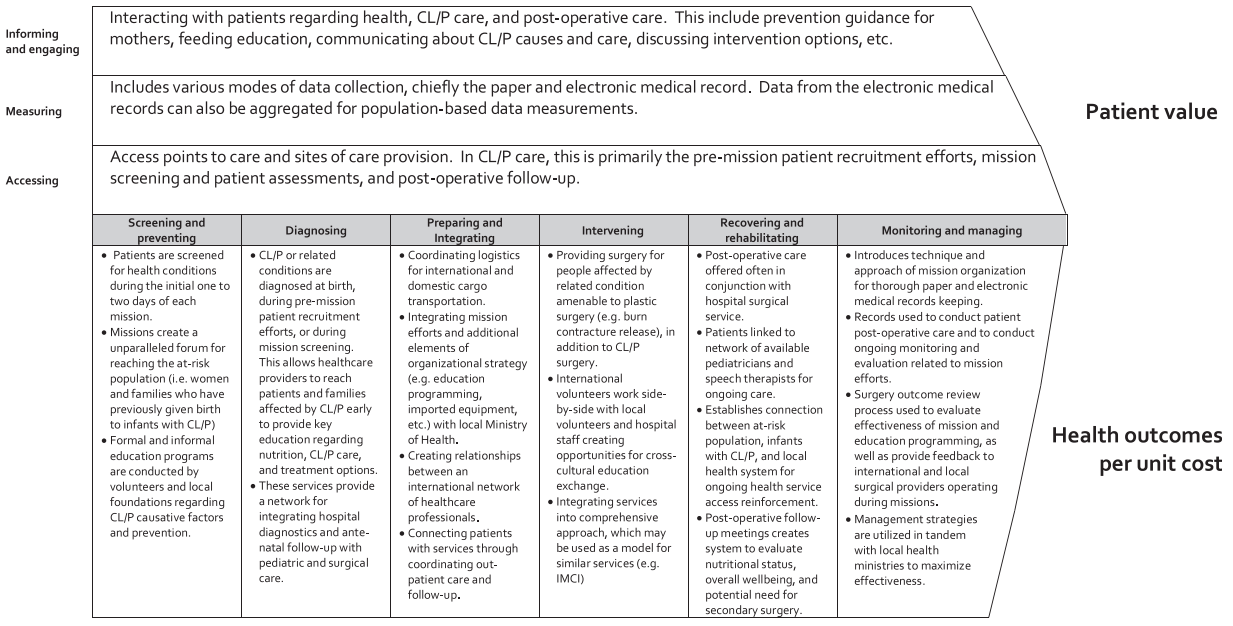

FIGURE 1. Care delivery value chain analysis of the mission model.

care delivery value chain tool to demonstrate a number of these effects across the continuum of care. These represent key areas with synergistic potential which can be capitalized upon by program planning and health systems' decision makers. Although this does not nearly exhaust the potential impact of the mission model, it offers a more comprehensive perspective on the mission's position within the health system.

THE DEVELOP-DISTORT DILEMMA

Not all downstream effects, however, are positive. One of the major concerns related to the mission model is its potential distortive effects on the health system and market. Any global health intervention and short-term interventions in particular have the ability to distort health markets and health systems.[32] Although interventions are typically promoted to help develop a health system or expand access, as communities adapt local health systems to these interventions, pre-existing providers may be crowded or priced out and systems altered to incorporate new delivery mechanisms, which may not be permanent or sustainable. This challenge embodies the Develop-Distort Dilemma.[32,33]

To understand how the mission model distorts the health system, we must first consider the mechanisms and systems currently in place to deliver surgical care for children with CL/P in LMICs. Unfortunately, outside of external actors and external compensating partners, in most LMICs, there are few services available to children born with CL/P, and it is not uncommon to live late into adulthood continually faced with the physical, mental, and social challenges associated with having an unrepaired CL/P.[5,31] Two billion people in the world lack access to basic surgical services; and among those who are able to access these services, the safety, timeliness, and effectiveness of these operations is often less than optimal.[2] Even in LMICs that are relatively higher-resourced and that have CL/P surgery providers, either plastic surgeons or general surgeons with additional training, the availability and accessibility of reconstructive surgery is generally low and may be associated with substantial costs. For this reason and because children with CL/P often come from lower socioeconomic backgrounds, the intrinsic, local market for CL/P surgery is exceedingly small.[33] Therefore, although introducing surgical missions may distort the market for CL/P surgery, crowding out existing providers, this effect is effectively negligible. Additionally, and possibly more importantly, the time and talents of existing providers edged out of CL/P surgery may easily be redistributed within the system. In other words, given the willingness of foreign medical teams and the availability of funding for such programs, international surgeons have a sort of comparative advantage for providing CL/P surgery relative to local surgeons.

We can, however, analyze the distortions and developmental effects of surgical missions on the greater surgical system within the respective country. This can be accomplished using the Distort-Develop Dilemma model developed by Peters et al.[32] Figure 2, adapted from Peters et al,[32] illustrates a prototypical health market and the various ways in which an intervention may develop or distort that market. Using this conceptual model to frame our understanding of the surgical mission, we can begin to perceive how missions may impact the surgical system. First, CL/P surgical missions act to directly reduce the burden of surgical disease. This reduces the burden on local surgeons who would otherwise be relied upon to provide CL/P surgery, and enables them to focus on other emergent and other essential surgical services. Often, acute and emergent surgical services exhaust a health system's surgical capacity leaving those with essential but non-emergent conditions unable to access care.[9,35] The temporary import of capacity through missions increases access for patients who have been unable to receive care. Additionally, this added capacity decreases structural

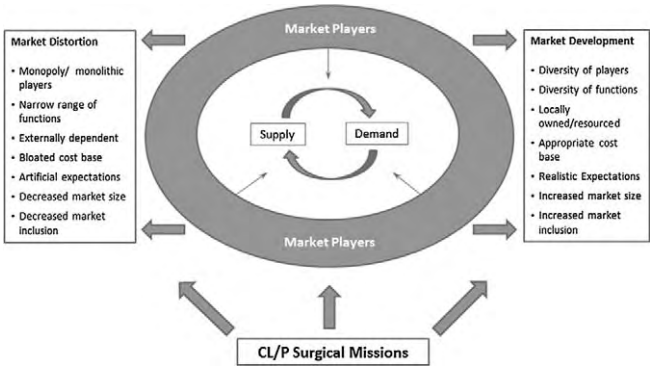

FIGURE 2. Develop-Distort Dilemma Framework. Adapted from Peters et al.[34].

and financial barriers that patients face in accessing surgical care.[5] Surgical missions further add to the diversity of services available by generating a gateway for cross-cultural education exchange and introducing new surgical practice techniques.[8,14] Surgical missions do not significantly affect overall cost base, market size, or market inclusion. Although missions are based on external funding, large international organizations have steadily increased the revenue base for these efforts from international donors and in-kind donations. Also, although missions are dependent on external inputs, when conducted responsibly they serve as a reliable approach to elective surgical service delivery in LMICs. With regard to the question of sustainability, the most pertinent question may be related to the sustained commitment of the implementing organization, as opposed to the future capacity to deliver services locally.[22] The notable distortion created in the market is the effect of foreign medical teams on patient expectations. In some instances this may have positive downstream impact, but it is an issue to be recognized and addressed when considering how to implement the mission model responsibly.

THE RESPONSIBLE MISSION MODEL

Overall, this discussion of the impact and effects of CL/P surgical missions in LMICs is dependent on the crucial assumption that missions are implemented responsibly. The concept of the responsible mission model has been discussed at length in the published literature and has also been internally developed over the 30-year institutional experience of Operation Smile.[30,31,34,36–38] Irresponsible implementation of the mission model to deliver CL/P surgical care in LMICs is faced with a number of pitfalls, which may jeopardize effective care delivery and patient safety, and may additionally disrupt the local health system.[6,34] From these discussions of responsibility in implementing the mission model, 3 major themes emerge: prioritizing patient safety, integrating into established local systems; and providing patient-centered care.

As the global surgery movement gains momentum, it is being increasingly recognized that although surgery has the potential to make a substantial positive impact in the lives of patients, the consequences of unsafe surgery are equally as great.[39,40] Patient safety is advocated for in both the United States and internationally under the common dictum of providing the same standard of care one would desire for a family member. Although this rule may serve as a guiding principle, institutionalized standards of care are essential. Operation Smile is led by their Global Standards of Care, which were developed by a consensus-based approach with stakeholders from more than 50 countries.[5,38] The entirety of these guidelines is beyond the scope of this discussion, but few key elements may be noted here.

One is the use of the World Health Organization Safe Surgery Checklist during each operation. This tool has been shown to reduce surgical complication rates by more than half when used internationally.[40] Next, standards for safe anesthesia, such as compulsory oxygen saturation monitoring and dantrolene availability, are critical.[2,41] Another item covered in the Global Standards of Care is patient follow-up. Patient follow-up is used to monitor and evaluate surgical outcomes, but its primary purpose is patient care and detecting surgical complications or signs of post-operative infection.[34] One final item to highlight is volunteer credentialing. The organization implementing missions has the responsibility to ensure that all volunteers are adequately qualified to participate in their respective role on surgical missions.[6,36] For CL/P surgical missions, this goes beyond collecting and checking licenses, but also includes determining whether CL/P surgery is within a surgeon's scope of practice. Operation Smile achieves this through a combination of licensure requirements and primary mission observerships, where surgical technique may be evaluated and endorsed for future mission participation.

The next major consideration for implementing the mission model responsibly is integrating programs into the local health system. Although traditionally considered ''vertical'' interventions, surgical missions add value across the health system.[8] To effectively capitalize on shared delivery systems and potential synergies within presently siloed health systems, system integration is key.[27] In addition to pragmatic reasoning for system integration, mission-based organizations practice as guests and are ethically-obligated to respect local systems.[34,36] Three major components of health system integration are: (1) acting in accordance with national and institutional regulations (eg, obtaining appropriate medical licensure, obeying customs regulations, and so on). (2) Respecting facility practices, standards, and customs within local hospitals to minimize the distortive effects and disruption potentially created by missions. (3) Partnering with locally based entities, which may be a permanent organization branch, a local health care facility, another NGO, or, ideally, the ministry of health. Partnership is perhaps the most important as it serves as the conduit for integration of the mission model into a health system.[8] Operation Smile has achieved this through forming local foundations in many countries and also by partnering international organizations and NGOs, such as UNICEF and Partners in Health in Rwanda. By doing this, the mission organization enables service delivery to be streamlined and the synergies listed above to be applied. It furthermore prevents the formation of service gaps in the wake of the mission. An essential component of these partnerships and of the responsible mission model is a sustained commitment to continuing to deliver care in the future.[14,36]

A final major consideration for the responsible mission model is one that largely remains to be developed—patient centeredness. Patient-centered care has been widely overlooked in the global surgery literature, yet it is crucial for ensuring that systems deliver high-value care to the patients we serve. Additionally, patient-centered care ensures the acceptability of the care delivery model and incorporates how services match patients' social and cultural expectations.[42] In many of the settings, where the mission model is used, value systems differ and demand-side factors are highly dissimilar. Research in evaluating the demand-side of the care delivery equation and how patients value care will likely have major implications for defining effectiveness and revising mission approaches.

This year Operation Smile has spoken with more than 500 patients and asked them about the barriers they have faced in accessing care. These data are currently being analyzed, but preliminary results are beginning to be applied to inform program strategies. For example, it is not unusual for patients to spend days travelling to an urban center to receive surgery during a mission. These travel costs have major implications in terms of access to surgery and follow-up care. Similarly, successful CL/P surgery outcomes are not limited merely to aesthetics and symmetry, but must incorporate indicators of patient satisfaction. Our patients come from a diverse range of backgrounds and formative experiences, and one cannot presume to comprehend the complexities of their lives. Instead, we must cultivate opportunities to listen to patients and commit to incorporating the patient perspective into service delivery efforts.

CONCLUSIONS

Medical missions serve as an effective platform from which to deliver safe, well-timed, and effective surgery in a way that is congruent with patient needs and constraints. Pressing disparities in the availability, accessibility, and affordability of safe, timely, and effective surgical care demand quick action and prompt solutions. That patients continue to seek surgical care at missions demonstrates that a gap in accessible care remains and that the need for direct care provision is present and pressing. This is not to say that long-term approaches to improve health system capacity are unimportant or mutually exclusive. It is widely accepted that enhanced training opportunities are necessary for responding to the global surgical workforce crisis and the significant demand for services in the long run.[9,16] During this time, however, the temporary expansion of the workforce through the mission model functions as a complementary solution in addressing the surgical needs of those who may otherwise face a heightened risk of premature death or be destined to live with substantial morbidity. The mission model used by Operation Smile and other mission-based organizations has been demonstrated to be an effective approach for delivering elective, yet timely, care to those requiring surgery today. This furthermore has broad benefits, developing the health system as a whole and producing only minimal distortive effects for present CL/P and general surgical systems.

We furthermore advocate for augmented efforts to better understand the value systems and demand-side factors within the communities we serve. Learning from patients about their barriers to care and understanding their expectations will inform organizations' efforts and will promote better programming practices. All of these must be done to develop an ever-more responsible mission model that answers to its patients first and integrates into local systems, as the human resources for health are cultivated to permanently erase disparities in surgical care.

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