Original Research Paper

Orofacial Clefts: Improving the Estimates for Global Birth Prevalence and Attributable Mortality

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ABSTRACT

Background: The overall purpose of the paper is threefold: (a) to improve estimated birth prevalence of orofacial clefts (OFC) with a particular focus on under-ascertainment in low resource settings; (b) to provide baseline data on infant mortality associated with OFC and (c) to highlight the value of pediatric surgery.
Methodology: Using CP/OFC ratio as an indicator of ascertainment because CP constitutes a standard percentage of total OFC independently of ethnic or inter-country differences using EUROCAT and ICBDSR congenital anomaly registries. Smile Train Express data was used to provide age at OFC repair and enabled the preparation of survival curves.
Results: Evidence-based country-specific estimates of the birth prevalence and outcomes of OFC have been developed for inclusion in the Modell Global Database of Congenital Disorders (MGDb). Adjustment of reported CP birth prevalence to the expected ratio raises estimated global OFC birth prevalence from the earlier figure of 1.1/1,000 births to 1.4/1,000 births. The Global Burden of Disease study estimates that a mere 0.024/1,000 attributable under-5 deaths (less than 0.05% of the global total in 2012) are due to OFC. However, data provided by Smile Train (STX) suggest 66-84% under-5 mortality with untreated OFC.
Conclusion: Under-ascertainment of the birth prevalence of OFC is common in lower resource settings, and their contribution to early mortality has been effectively overlooked globally. Targeted intervention by STX, an international NGO, has greatly reduced associated mortality and disability.

Keywords: Orofacial Clefts, Birth Prevalence, Ascertainment, Mortality, Pediatric Surgery.
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Introduction

Oro-facial clefts (OFC) are among the commonest congenital malformations: reported birth prevalence ranges by country from 0.3 to 2/1,000 births, with an average global birth prevalence of over 1 per 1,000. OFC include a wide range of defects and sub-phenotypes [1-2] but for epidemiological purposes they are usually bundled into two groups, cleft lip with or without cleft palate (CL(P)) and cleft palate (CP). These groups are generally viewed as distinct entities because

they arise at different times during embryonic development and are affected differently by genetic and environmental factors. From an epidemiological point of view there is also an important pragmatic difference: CL(P) is a sentinel phenotype - "a disorder of considerable frequency that is conspicuous at birth, is accurately diagnosable with minimal clinical effort, and so offers a relatively high probability of ascertainment" [3]. By contrast CP is easily missed without specific training and is often under-ascertained [4]. It is therefore reasonable to enquire how far under-ascertainment may contribute to inter-country differences in reported birth prevalence. In most congenital anomaly registries with recognised high ascertainment CP accounts for 30-50% of OFC, regardless of total reported birth prevalence. The proportion of CP has therefore been suggested as an indicator of ascertainment [5]. We found that application of this indicator suggests frequent under-ascertainment of CP and so of total OFC.

In MGDb attributable mortality is calculated from estimated survival with optimal care and in the absence of care, and the proportion of the population with access to care [6], but we could find no published data on survival in the absence of care. To fill this gap, we constructed a "no-care" survival curve based on unpublished data from an Indian survey [7] and statistical data provided by Smile Train an international NGO that supports surgical repair of OFC via their Smile Train Express database [8]. The Smile Train data also enabled us to estimate the effect of this NGO on global early mortality due to OFC.

In 2015 the Lancet commission on Global surgery reported that 5 billion people worldwide lacked access to surgical care [9], and it was estimated that 1.7 billion were children and adolescents [10]. Here we describe the methods used to obtain more accurate ascertainment estimates, and their effect on the estimated global birth prevalence of OFC and attributable early mortality in the absence of surgical intervention.

Methodology

Sources of OFC birth prevalence data

The Modell Global Database of Congenital Disorders (MGDb) [11] was used to address two questions raised during this undertaking, namely (1) the reliability of published estimates of affected birth prevalence and (2) the true contribution of OFC to early mortality.

Data on baseline birth prevalence of OFC was obtained from two systematic reviews [12, 13] and two "umbrella" registries, the European Surveillance of Congenital Anomalies and Twins network [14] and the International Clearing House for Birth Defect Surveillance and Research [15] (ICBDSR). European Registration of Congenital Anomalies and Twins (EUROCAT) collects data from registries in 21 European countries. The 1985-2005 ICBDSR dataset used included additional data for 21 non-European countries.

Together these sources contained observational data for 57 countries covering all WHO regions. Using these data, we (1) developed country-specific estimates of baseline birth prevalence and outcomes of non-syndromic and isolated OFC by filling gaps with near-neighbour estimates; (2) assessed potential under-ascertainment using the proposed indicator, and (3) adjusted the proportion of CP to the rate expected with full ascertainment.

Quality of ascertainment: use of EUROCAT data

EUROCAT demonstrated high ascertainment in most participating registries [16-17] and produced a Special Report on country-specific data for total, non-syndromic, associated, and isolated OFC [18]. Despite a wide range of affected birth prevalence, the proportions of different groups are relatively consistent. Table 1 shows EUROCAT average rates based on this report. On average 18% of OFC are syndromic, around 19% of non-syndromic clefts are associated (over half with malformations that cause early death in the absence of care) [19]. In well ascertained registries the proportion of CP was between 30 and 40% of both non-syndromic and isolated OFC regardless of birth prevalence. Similar rates apply for most other congenital anomaly registries in high resource settings.

Table 1. Average birth prevalence of OFC in Europe 1980-96 (EUROCAT 2000). (Total birth prevalence includes live births and foetal deaths/stillbirths. Rates particularly relevant for this report are highlighted)

Group of clefts	Rate /1,000 births					% of total				Isolated % non-syndromic
	Total	Syn-dromic	Non-syn-dromic	Associ-ated	Isol-ated	Syn-dromic	Non-syn-dromic	Assoc-iated	Isol-ated	
Cleft palate (CP)	0.62	0.17	0.45	0.11	0.34	27	73	18	55	75
Cleft lip +/- cleft palate CL(P)	0.9	0.1	0.80	0.14	0.66	11	89	16	73	83
Total OFC (OFC)	1.52	0.28	1.24	0.25	1.00	18	82	16	66	81
	Per cent CP									
CP % of total OFC	41	61	36	44	34					
CP % of CL(P)	69	170	56	79	52					

A more recent analysis of all EUROCAT OFC data from 1980 to 2012 and covering 26.8 million births gave an average of 40% CP with a range from 30 to 50% (Figure 1) and this was accepted as a global indicator of quality of ascertainment.

Figure 1 shows that regardless of differences in birth prevalence, in EUROCAT data for most countries CP constitutes 30-50% of non-syndromic OFC.

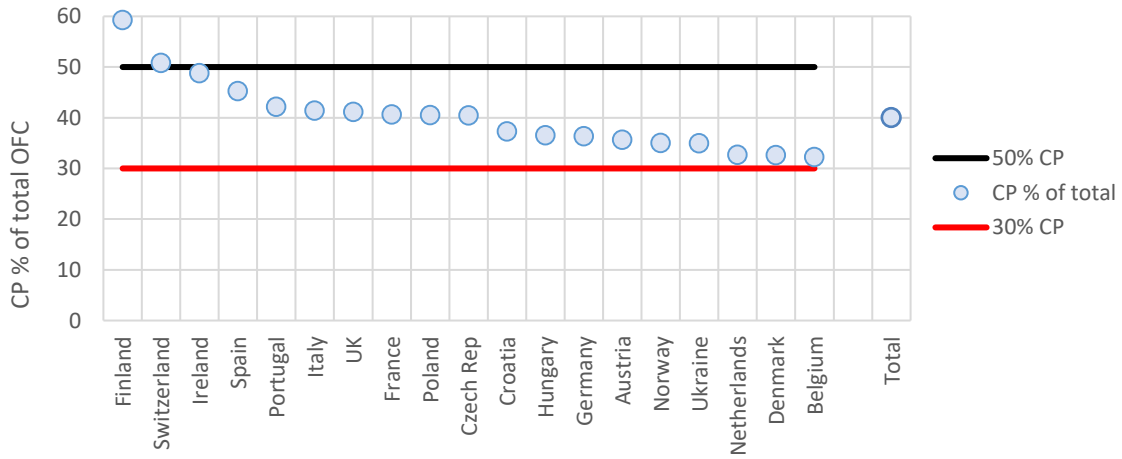


Figure 1: Countries with registries reporting to EUROCAT. Cleft palate as per cent of total non-syndromic OFC, 1980-2012. (Rates for Malta and Bulgaria are excluded because of small numbers.)

Estimating The Effect of Interventions

In calculating country-specific affected live birth prevalence and outcomes it is necessary to allow for the effects of folic acid food fortification, termination of pregnancy following prenatal diagnosis, and attributable fetal death/stillbirth.

- While demonstrating heterogeneity, the available evidence indicates that mandatory folic acid food fortification reduces the birth prevalence of OFC by approximately 20% of the local per cent reduction in neural tube defects [20-23]. We believe this to be a justifiable, albeit conservative adjustment of risk in OFC in light of the latest and best available evidence [24]. An adjustment for this effect, based on reports from the Food Fortification Initiative[1] on the global deployment of mandatory fortification is included in our calculation of the actual birth prevalence of OFC in 2010-14.
- We have made no allowance for termination of pregnancy for isolated OFC. In Europe in 1980-96 an average of 27% of CL(P) and 7% of CP were detected by fetal anomaly scanning: around 10% of these pregnancies were terminated, but only 5.5% of terminations (less than 1% of total cases) were for isolated clefts [18]. A similarly low termination rate is also reported from the USA [25]. Anecdotal reports suggest that prenatal diagnosis of an OFC in a lower-resource setting can result in termination of pregnancy. However, we could not allow for this in the absence of quantitative data.
- We have assumed that isolated OFC are not a cause of fetal death. EUROCAT data show an average 1.3% fetal death rate for non-syndromic OFC, but it seems likely that most are associated cases, as is the case for termination of pregnancy.

Outcomes for live births: survival and disability

The no-care situation. Sources for the construction of a no-care survival curve were (a) data from a large unpublished survey conducted in India before the start of Smile Train intervention [7] and (b) administrative data on operations supported by Smile Train between 2000 and 2010 in Bangladesh, China, India, Pakistan and The Philippines. The method is described in the results section. All survivors with an untreated OFC live with severe disability.

Optimal care. In high resource settings the great majority of affected infants are detected and referred for corrective surgery but there is still significant residual disability and mortality. In Hungary in the 1970s 20% of cases lived with residual disability [26], and in the UK today around 12% have long-term cosmetic and/or communication problems [27-29]. Scandinavian studies of isolated OFC show 98% survival and a significantly increased rate of early death, and only 71% success in building a family relative to the population norm [30-32]. The "optimal care" survival curve used here (Figure 2) is based on the 2004 Danish report by Christensen and colleagues [30].

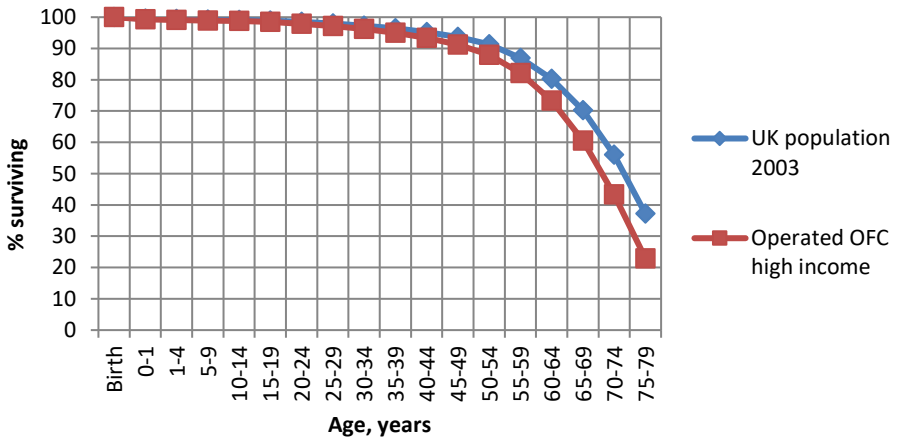


Figure 2: Survival with operated OFC in high income setting. Standardised mortality ratio = 1.4 at all ages (Christensen et al 2004).

Comparison with other mortality estimates

The Global Burden of Disease study (GBD) publishes numerical estimates of deaths attributable to disorders included in ICD10 chapter XVII (congenital malformations, deformations and

chromosomal anomalies) by age group and country [33]. These include estimates of deaths attributable to OFC. To compare GBD and MGDb estimates of attributable under-5 deaths GBD estimates for 2012 were converted to rates /1,000 births using World Population Prospects (WPP) estimates for annual births in 2010-14 [34].

Results

Application of global quality indicator to data from other sources

The proposed global indicator of ascertainment was then applied to data for 35 non-European countries included in the Kadir 2016 Report [13]. The proportion of CP falls below 30% in more than 50% (Figure 3). This suggests that under-ascertainment of CP is common, particularly in lower-resource settings.

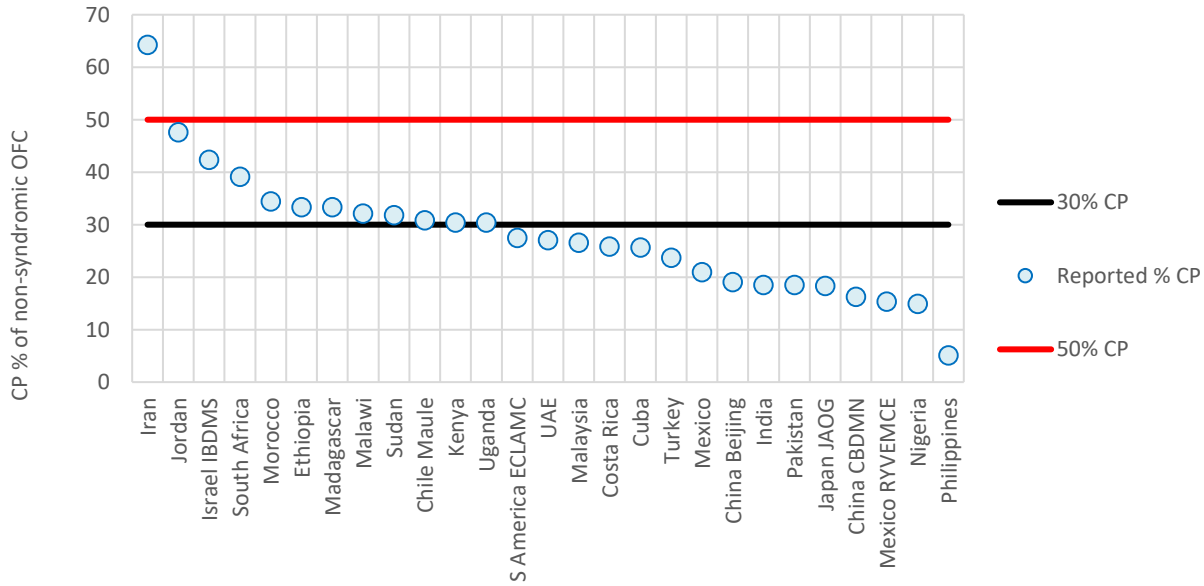


Figure 3: CP as % of total non-syndromic OFCs in ICBDSR and Kadir et al.,2017.

Is it possible that the low proportion of CP reported from some countries represents reality? To address this question, we compared the proportion of isolated CP in five large lower-income countries in publications from the two systematic reviews with data on numbers and types of operation supported by Smile Train data (STX) (Table 2). The proportions of CP in the STX are in broad agreement with EUROCAT and higher than those based on the literature.

Table 2: Comparison of proportion of isolated cleft palate (CP) based on the literature, with rates from Smile Train (STX) surgical data.

Country	Total isolated OFC per 1000 LB based on data from systematic reviews	CP % of non-syndromic OFCs		Smile Train, multiple of literature
		Systematic reviews	Smile Train	
China	2.31	15	63	4.2
Philippines	2.56	5	37	7.3
India	1.73	19	45	2.4
Bangladesh	1.73	19	31	1.7
Pakistan	1.73	19	49	2.6

We conclude that it is reasonable to use the proportion of CP to total non-syndromic OFC as an indicator of ascertainment: a ratio of 30-50% suggests reasonable ascertainment of CP, while less than 30% suggests under-ascertainment of CP and so of total OFC.

Adjustment of estimated baseline birth prevalence

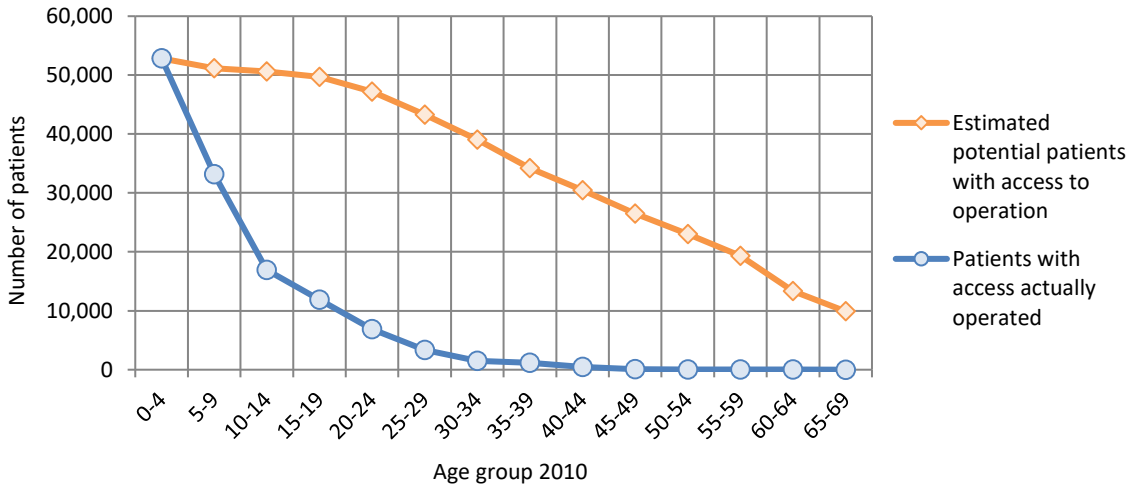
The MGDb generates estimates for isolated congenital malformations because outcomes must be expressed in terms of affected individuals. Our original MGDb estimates for isolated OFC were derived from the umbrella registries and the literature. Here we calculate the effect of adjustment for under-ascertainment of CP on these rates (Table 3). Similarly, rates for non-syndromic CP can be adjusted to the average EUROCAT rate of 56% of non-syndromic CL(P).

Table 3: Adjustment of estimated birth prevalence of isolated orofacial clefts, showing the effect of under-ascertainment of CP

WHO region	Reported Isolated CL(P) /1,000 births	Reported rate /1,000 births		Adjusted rate /1,000 births		Adjusted multiple of reported	
		Isolated CP	Total isolated OFC	Adjusted isolated CP	Adjusted total isolated OFC	Isolated CP	Total isolated OFC
EUR	0.7	0.4	1.1	0.36	1.06	0.9	0.96
AMR	1.11	0.48	1.59	0.58	1.68	1.2	1.06
EMR	0.67	0.25	0.92	0.35	1.02	1.4	1.11
AFR	0.54	0.15	0.69	0.28	0.82	1.89	1.19
SEAR	1.00	0.21	1.21	0.52	1.52	2.46	1.26
WPR	1.48	0.26	1.74	0.77	2.25	2.96	1.29
World	0.92	0.25	1.17	0.48	1.4	1.88	1.19
W. Europe	0.68	0.32	1.01	0.35	1.04	1.09	1.03

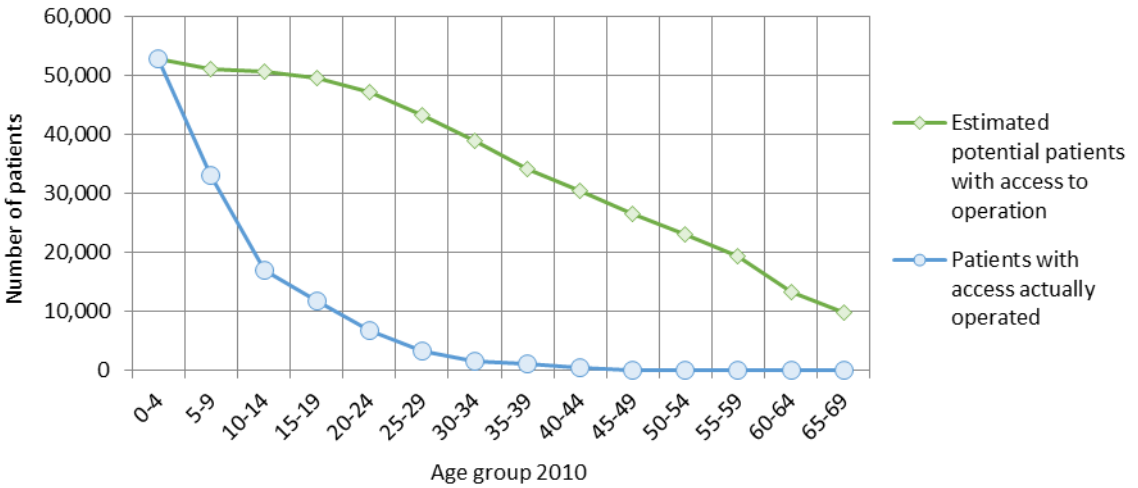
Mortality due to OFC

The second major issue in relation to OFC is one that differs significantly in low resource compared to high resource settings – survival in the absence of care. Evidence informing this issue has been derived from 3 sources (1) the Tata survey (2) the Tamil Nadu survey and (3) Smile Train data. Before initiating their operations in India Smile Train conducted a large population-based survey of OFC in representative districts of three states that became known as the Tata survey [7]. This identified 2,122 living individuals with OFC. Of these only 5% had CP, suggesting serious under-ascertainment and high early mortality with this defect. The patients' age distribution (Figure 4) indicated an approximately 80% loss in the first five years but a good life-expectancy for



those who survived past this age. Face-to-face interviews showed that parents consider operation to be necessary for affected individuals to marry, but only 25% of the surviving patients had had an operation. The reality of "catastrophic expenditure" combined with societal pressures, beliefs and stigma were the main reasons for children remaining unoperated.

Figure 4: Smile Train data for India 2000-9. The lower line shows the age distribution of those actually operated in these 10 years. The upper line shows the number who would have access to operation if their survival equalled the population norm: the curve reflects the 2000 age distribution of the Indian population (United Nations WPP 2015). The gap between the two decreases with age.



The Tamil Nadu surveys. Two Indian studies reported by Kadir et al. in 2016 [13] found a baseline birth prevalence of non-syndromic OFC of 1.0 and 1.3 /1,000 – an average of approximately 1.34/1,000 when adjusted for under-ascertainment of CP. A survey of visible congenital anomalies in 11.87 million children aged 0-15 in Tamil Nadu [35] identified 0.506 /1,000 with an OFC (38% of expectation). The survey showed that most of those aged 1-14 had surgical correction providing they had access to it, and two-thirds of the survivors (0.339/1,000) had already had the defect repaired. This leaves an estimated 0.167/1,000 with an unoperated OFC - 12% of the estimated unoperated group. One year later, after the arrival of Smile Train, 93% of survivors had had a repair.

Smile Train data

Smile Train administrative data show that in the 10 years 2000 to end 2009 over a quarter of a million individuals with OFC were operated with Smile Train support in the five countries shown in Table 4.

Table 4: Number of patients operated with Smile Train support in five countries (2000 – 2009)

Country	Start of Smile Train intervention	Number operated by end 2009
India	2000	137,480
China	2001	107,544
Bangladesh	2002	8,608
Philippines	2002	6,912
Pakistan	2003	9,203
Total to end 2009		269,747

These data enable the construction of a baseline survival curve. The calculation assumes that when operation is known to be available to everyone affected, free of charge, most of those below marriageable age will have the defect repaired (both the above surveys confirm this). In practice over 80% of operations were for children under fifteen, but operations were also performed for all ages up to 70 years old, confirming access regardless of age. In this situation there are two possible reasons for "missing" cases – unwillingness to undergo operation or absence due to death. The evidence supports the proposition that early death is the commonest explanation for missing cases below marriageable age, though reluctance may contribute to the low frequency of operation for older patients.

With the above assumptions the number of patients actually operated through Smile Train equals the number of living but hitherto unoperated patients in each age group with access to the service. A comparison of the age profile of those operated with the age profile of the general population therefore reflects the survival of unoperated individuals. **Figure 4** illustrates the method using India as an example. The lower curve shows numbers in each 5-year age group actually operated, and the upper curve shows numbers who would be available for operation if survival equalled the population norm.

The gap between potential numbers and numbers actually operated – "missing cases" - may be taken to represent mortality due to OFC. The figures for those born in the 10 years 2000-09 reflect the progressive intervention of SmileTrain, but figures for those aged 10-14 or over in 2010 represent survival to this age with an unoperated OFC. **Figure 5** compares the derived survival curve of this group with that from the Tata survey.

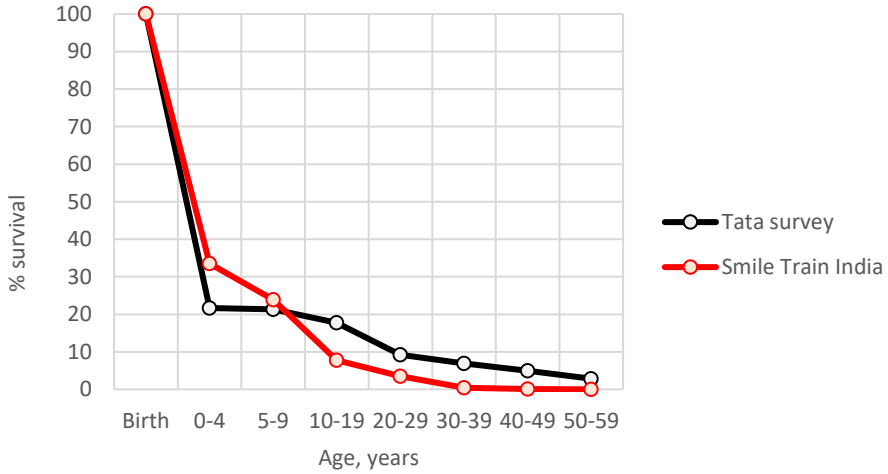


Figure 5: Comparison of survival with unoperated OFC in India derived from the Tata survey, and Smile Train data on year of birth at operation. The curves are similar. The lower survival estimate at older ages in the Smile Train curve may reflect reluctance of older survivors to come forward for operation.

When survival is estimated in this way the result is similar in all five countries that Smile Train operates in (Table 5): before intervention by the NGO at least 60% of unoperated affected children had died by five years of age, and over 75% had died by 10 years of age. Note that the calculations apply for the portion of the population with access to medical care providing it is free of charge: mortality is likely to be even higher among those without such access.

Clearly these estimates are approximations. However, they are mutually consistent. All indicate very high early mortality with OFC in the absence of access to surgery. Based on this evidence we estimate an average 65% infant mortality and 82% under-5 mortality with OFC in the absence of care.

Table 5: Estimated survival with unoperated OFC in five countries with Smile Train intervention

Age group	Bangladesh	Pakistan	India	Philippines	China
Birth	100	100	100	100	100
0-4	40.1	34.0	33.5	21.9	15.7
5-9	22.0	23.8	23.9	11.1	11.2
10-14	13.5	15.8	14.6	5.2	8.3
15-19	7.5	8.2	7.8	2.6	2.5
20-24	4.0	4.3	3.9	1.6	1.1
25-29	3.8	3.9	3.5	0.5	0.7
30-34	1.5	1.9	1.6	0.3	0.4
35-39	0.4	0.9	0.4	0.5	0.1
40-44	0.4	0.4	0.2	0.1	0.1
45-49	0.6	0.4	0.1	0.2	0.1
50-54	0.0	0.0	0.1	0.0	0.0
55-59	0.0	0.0	0.0	0.0	0.0

Effect of targeted intervention by an NGO

In MGDb early mortality is calculated from mortality with no care and optimal care, and estimated access to care based on local infant mortality. Disorder-specific charities can increase access to care and so reduce under-5 mortality for certain disorder groups, but it is rarely possible to allow for such effects due to lack of data. Exceptionally, we were able to include the estimated effect of the Smile Train NGO when calculating actual global under-5 mortality due to OFC: the charity has reduced estimated under-5 deaths due to OFC by more than 25% (Table 6).

Table 6: Estimated effect of the intervention of the Smile Train NGO on under-5 mortality due to oro-facial clefts: estimates for 2010. (Revised Feb 2020, with allowance for under-ascertainment of CP and 70% access in China)

WHO region	Annual births 1,000s	OFC births /1,000 [1]	OFC under-5 deaths /1,000			Smile Train % reductn	OFC Actual annual births	Estimated annual under-5 deaths		
			If no Smile Train	Smile Train reductn	With Smile Train			If no Smile Train	Smile Train reductn	With Smile Train
AFR	34,647	0.46	0.334	0.2	0.327	1.9	16,060	11,555	214	11,341
AMR	15,319	1.45	0.455		0.455		22,170	6,971		6,971
EMR	16,906	1.01	0.597	0.8	0.550	7.8	17,087	10,087	785	9,302
EUR	11,296	1.05	0.074		0.074		11,858	840		840
SEAR	37,304	1.41	0.916	9.6	0.658	28.2	52,543	34,181	9,630	24,551
WPR	24,368	2.15	0.612	10.0	0.203	66.8	52,428	14,908	9,960	4,948
World	139,840	1.23	0.562	0.147	0.414	26.2	172,146	78,543	20,589	57,954

[1] *OFC births /1,000 allowing for the effect of folic acid food fortification in 2010-14. Deaths are estimated on the basis of this birth prevalence.*

Table 7: Estimated contribution of OFC to under-5 mortality in 2010-14, including the estimated effect of Smile Train

WHO region	Under-5 deaths /1,000	Estimated % access to care	OFC under-5 deaths /1,000		OFC % of total under-5 deaths		% reduction in total under-5 deaths
			If no Smile Train	With Smile Train	If no Smile Train	With Smile Train	
AFR	96.4	8	0.334	0.327	0.35	0.34	0.01
AMR	20.4	63	0.455	0.455	2.23	2.23	
EMR	58.3	30	0.597	0.550	1.02	0.94	0.14
EUR	13.5	88	0.074	0.074	0.55	0.55	
SEAR	47.1	19	0.916	0.658	1.95	1.40	1.16
WPR	16.0	66	0.612	0.203	3.82	1.27	16.0
World	49.6	37	0.562	0.414	1.13	0.84	0.60

The improbably high 16% estimated reduction in the Western Pacific Region suggests limitations in the available demographic and prevalence data.

Table 7 shows the estimated contribution of OFC to global under-5 deaths and the effect of Smile Train. The figures indicate that OFC would have been responsible for at least 1.1% of under-5 deaths in 2010-14, but when the effect of Smile Train is included, the estimate falls to less than 0.8%. Globally, by targeting a conspicuous and potentially lethal congenital malformation, this single NGO is estimated to have reduced global under-5 deaths by at least 0.6%. This estimate appears relatively reliable in view of the solid nature of the Smile Train data. Since Smile Train is not the only international charity supporting treatment for OFC the true current contribution of OFC to global under-5 death is probably significantly lower.

Comparison with Global Burden of Disease estimates

The GBD global estimate (0.024/1,000 = 3,358/year) is less than 5% of the MGDb estimate. The extraordinary difference indicates that mortality due to OFC has hitherto been largely overlooked in global assessments of the burden of disease.

Discussion

Ascertainment

The reported birth prevalence of OFC differs significantly between populations. Though differences in local environmental and genetic factors are known to play a part, it is also necessary to enquire into completeness of ascertainment. Under-ascertainment of congenital malformations is common even in dedicated congenital anomaly registries [4, 36]. The likelihood of under-ascertainment is lowest for severe malformations that are obvious at birth such as anencephaly and higher for less obvious malformations such as low-level spina bifida. For this reason, EUROCAT uses the reported proportion of anencephaly as an indicator of ascertainment of neural tube defects: a higher proportion than 40% suggests under-ascertainment of spina bifida and encephalocele, a lower proportion suggests under-ascertainment of anencephaly. Similarly, we explored the use of the proportion of CP as an indicator of ascertainment of OFC, as proposed by Woolf in 1963 [5]. The congenital anomaly registries reporting to EUROCAT are obliged to demonstrate multiple source ascertainment. Although the reported birth prevalence of non-syndromic OFC ranges from over 1.75/1,000 in Northern Europe to around 1.1/1,000 in the South, CP usually represents 30-50% of total OFC, and the same generalisation applies for most other registries in high resource settings. We conclude that the ratio of CP to total OFC is a valid (though approximate) indicator of quality of ascertainment. If the proportion of CP in all reports is adjusted to the EUROCAT 32% average, the result is an 88% increase in global birth prevalence of CP and a 19% increase in global birth prevalence of total isolated OFC, from 1.17 to 1.4/1,000 births, and therefore globally

almost 50% of CP may be missed at birth. This raises the question about the extent to which similar under-ascertainment might apply to other types of congenital malformation

Attributable mortality

The demonstration that untreated OFC are associated with 75-80% early mortality leads to the conclusion firstly, that global under-5 mortality due to OFC would be 1/1,000 in the absence of any access to care; secondly, that in 2010-14 with access to locally available surgical care it would be around 0.51/1,000; thirdly by having access to Smile Train surgical data, the evidence demonstrates that this potential mortality has been reduced to 0.32/1,000 by the intervention of Smile Train – a 38% reduction.

The data that enables more precise estimates of under-ascertainment in low and middle income country (LMIC) settings comes from well ascertained figures from high resource settings, and adjustment of reported CP birth prevalence to the expected ratio raises estimated global OFC birth prevalence from the earlier figure of 1.1 /1,000 births to 1.4/1,000 births.

Estimation of attributable early mortality was made possible by data provided by Smile Train (an international NGO that supports operation for OFC in lower-resource settings) which suggest under-5 mortality with untreated OFC of up to 84%. Between 2010-14 about 60% of the world population had no access to treatment, so that OFC would cause around 104,700 under-5 deaths in the absence of additional intervention, but in this 2010-14 period Smile Train intervention offset the high mortality rate by the provision of surgical care and this is of global significance. This serves to demonstrate the value of paediatric surgery in the survival of infants and ultimately the rehabilitation of individuals born with surgically correctable deformities.

These ascertainment and mortality issues establish CLP as a sentinel defect and provide a basis for a Health Economics assessment that will seek to quantify the cost benefit of paediatric surgery and offsetting both mortality and disability, with a view to influencing policy makers and addressing one of the most anomalous global inequities. The question that should be asked is ..."How many additional life years does paediatric surgery provide (per head of birth cohort) and furthermore how many years of normal life does surgery confer in a population where (a number) of children are born with CLP in a given year". LMIC governments and policy makers need to appreciate the rationale and potential financial and social impact of paediatric surgery, and the immediate challenge will be to extend this to include the full range of congenital anomalies, in alignment with SDG3 and universal health coverage.

Conclusions

This manuscript based on the Modell Global Database of Congenital Disorders (MGDb) provides, for the first time a LMIC perspective to the global birth prevalence of OFC, and a description of the evidence base to support this.

This has enabled a global picture of the true incidence of OFC and base-line survival curves based on surgical data from LMICs highlight the inequality in access to primary surgical care and the effects on infant mortality. We estimate that in 2010-14 about 60% of the world population had no access to treatment, so that OFC would cause around 104,700 under-5 deaths in the absence of additional intervention, but in this period Smile Train intervention averted an estimated 25,360 early deaths, reducing attributable OFC under-5 mortality from 1.4% to 1% of the global total.

It also highlights the very significant inequalities that exist in the developing world setting in the registration and ascertainment of OFC and in particular detecting and reporting of isolated CP in infants which explains the dearth of accurate data.

By raising awareness of the effects of access to surgical care on mortality and survival, the value of paediatric surgery as not only a life transforming but also a life-saving procedure is highlighted.

References

1. Mossey PA, Little J, Munger RG, Dixon MJ, Shaw WC. Cleft lip and palate. Lancet 2009;374: 1773–85.
2. McBride WA, McIntyre GT, Carroll K, Mossey PA. Subphenotyping and Classification of Orofacial Clefts: Need for Orofacial Cleft Subphenotyping Calls for Revised Classification. Cleft Palate Craniofac J 2016;53(5);539–49.

3. Czeizel A. The Hungarian surveillance of new mutations: lack of detectable increase in the occurrence of indicator conditions caused by germinal mutations in Hungary following Chernobyl nuclear power plant accident. Hum Genet 1989;82:359-66.
4. Kubon C, Sivertsen A, Vindenes H A, Abyholm F, Wilcox A, Terje Lie R. Completeness of registration of oral clefts in a medical birth registry: a population-based study. Acta Obstetr Gynecol 2007;86:1453-57.
5. Woolf CM, Woolf RM, Broadbent TR. A genetic study of cleft lip and palate in Utah. Am J Hum Genetics 1963;15(2):209-15.
6. Blencowe H, Moorthie S, Darlison MW, Gibbons S, Modell B. Methods to estimate access to care and the effect of interventions on the outcomes of congenital disorders. Congenital Disorders Expert Group. J Community Genet 2018;9(4):363-76.
7. Siva Raju S. In search of a smile. Study of Children born with Cleft Lips and Palates in India. Unit for Urban Studies, Tata Institute of Social Sciences Mumbai. (Prepared for Impact India Foundation, Mumbai. Sponsored by The Smile Train. New York, USA.) December 2000.
8. Smile Train Express Database: https://www.smiletrainexpress.org/ 31st July 2022.
9. Meara JG, Greenberg SL. The Lancet Commission on Global Surgery Global surgery 2030: evidence and solutions for achieving health, welfare and economic development. Surgery 2015;157(5):834-5.
10. Mullapudi B, Grabski D, Ameh E, Ozgediz D, Thangarajah H, Kling K, Alkire B, Mearae J, Bicklera S. Estimates of number of children and adolescents without access to surgical care. Bull WHO 2019;97(4).
11. Moorthie S, Blencowe H, W Darlison M, Lawn JE, Mastroiacovo P, Morris JK, Modell B. Congenital Disorders Expert Group. J Community Genet 2018;9(4):347-62.
12. Mossey PA, Little J. Chapter 12: Epidemiology of oral clefts: an international perspective. In Wyszynski DF (Ed) Cleft lip and palate. From origin to treatment. pp127-158. Oxford University Press: UK; 2012.
13. Kadir A, Mossey PA, Blencowe H, Moorthie S, Lawn JE, Mastroiacovo P, Modell B. Systematic Review and Meta-Analysis of the Birth Prevalence of Orofacial Clefts in Low- and Middle-Income Countries. Cleft Palate Craniofac J 2017;54:571-81.
14. EUROCAT: https://eu-rd-platform.jrc.ec.europa.eu/eurocat_en 31st July 2022
15. International Clearing House for Birth Defect Monitoring Systems (ICBDSR) www.icbdsr.org
16. Moorthie S, Blencowe H, Darlison MW, Lawn J, Morris JK, Modell B, Congenital Disorders Expert Group, Bittles AH, Blencowe H, Christianson A, Cousens S, Darlison MW, Gibbons S, Hamamy H, Khoshnood B, Howson CP, Lawn J, Mastroiacovo P, Modell B, Moorthie S, Morris JK, Mossey PA, Neville AJ, Petrou M, Povey S, Rankin J, Schuler-Faccini L, Wren C, Yunnis KAJ. Estimating the birth prevalence and pregnancy outcomes of congenital malformations worldwide. Commun Genet 2018;9(4):387-96.
17. Tucker FD, Morris JK, JRC Management Committee, Neville A, Garne E, Kinsner-Ovaskainen A, Lanzoni M, Loane MA, Martin S, Nicholl C, Rankin J. EUROCAT: an update on its functions and activities. J Commun Genet 2018;9:407-10.
18. EUROCAT Special Report. EUROCAT and Orofacial Clefts: The epidemiology of Orofacial Clefts in 30 European Regions; 2000. www.eurocat.ulster.ac.uk/pdf/Orofacial-Report.pdf.
19. Rittler M, Lopez-Camelo JS, Castilla EE, Bermejo E, Cocchi G, Correa A, Csaky-Szunyogh M, Danderfer R, De Vigan C, De Walle H, da Graca Dutra M. Preferential associations between oral clefts and other major congenital anomalies. Craniofacial J 2008;45(5):525-32.
20. Simmons CJ, Mosley BS, Fulton-Bond CA, Hobbs C. Birth defects in Arkansas: is folic acid fortification making a difference? Birth defects research (Part A) 2008;70:559-64.
21. Canfield MA, Collins JS, Botto LD, Williams LJ, Mai CT, Kirby RS. Changes in the birth prevalence of selected birth defects after grain fortification with folic acid in the United States: findings from a multi-state population-based study. Birth Defects Res A Clin Mol Teratol 2005;73: 679-89.
22. Yazdy MM, Honein MA, Xing J. Reduction in orofacial clefts following folic acid fortification of the U.S. grain supply. Birth Defects Res A Clin Mol Teratol 2007;79:16-23.
23. Song Li, Chao Anna, Li Zhu, Moore A, Liu Yinhui, Zhu Jianghui, Erickson JD, Hao Ling, Berry RJ. Folic acid use and non-syndromic OFC in China. A prospective cohort study. Epidemiology 2012;23:1-10.
24. Zhou Y, Sinnathamby V, Yu Y, Sikora L, Johnson CY, Mossey PA, Little J. Folate intake, markers of folate status and oral clefts: An updated set of systematic reviews and meta-analyses. Birth Defects Research. 2020;112:1699–719.
25. Yazdy, MM, Honein, MA, Rasmussen SA, Frias JL (2007). Priorities for future public health

research in orofacial clefts. Cleft Palate Craniofac J 2007;44(4):351-7.
26. Czeizel A, Sankaranarayanan K. The load of genetic and partly genetic disorders in man. 1. Congenital anomalies: estimates of detriment in terms of years of life lost and years of impaired life. Mutation Research 2007;128:73-103.
27. Williams AC, Bearn D, Mildinhall S, Murphy T, Sell D, Shaw WC, Murray JJ, Sandy JR. Cleft lip and palate care in the United Kingdom--the Clinical Standards Advisory Group (CSAG) Study. Part 2: dentofacial outcomes and patient satisfaction. Cleft Palate Craniofac J 2007;38(1):24-9.
28. Sell D, Grunwell P, Mildinhall S, Murphy T, Cornish TA, Bearn D, Shaw WC, Murray JJ, Williams AC, Sandy JR. Cleft lip and palate care in the United Kingdom--the Clinical Standards Advisory Group (CSAG) Study. Part 3: speech outcomes. Cleft Palate Craniofac J 2001;38(1):30-7.
29. Bearn D, Mildinhall S, Murphy T, Murray JJ, Sell D, Shaw WC, Williams AC, Sandy JR. Cleft lip and palate care in the United Kingdom--the Clinical Standards Advisory Group (CSAG) Study. Part 4: outcome comparisons, training, and conclusions. Cleft Palate Craniofac J 2001;38(1):38-43.
30. Christensen K, Juel K, Herskind AM, and Murray JC. Long term follow up study of survival associated with cleft lip and palate at birth. BMJ 2004;328(7453):1405-11.
31. Skjaerven R, Wilcox AJ, Lie R. A population-based study of survival and childbearing among female subjects with birth defects, and the risk of recurrence in their children. New Engl J Med 1999;340:1057-62.
32. Lie R, Wilcox AJ, Skjaerven R. Survival and reproduction among males with birth defects, and risk of recurrence in their children. JAMA 2001;285:755-60.
33. Poenaru D, Lin D, Corlew S. Economic Valuation of the Global Burden of Cleft Disease Averted by a Large Cleft Charity World J Surg 2016;40:1053–9.
34. United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2015 Revision. http://esa.un.org/unpd/wpp/DVD/
35. Sridhar K. A community-based survey of visible congenital anomalies in rural Tamil Nadu. Indian J Plast Surg 2009;42:S184-91.
36. Czeizel AE. Registers of congenital abnormalities. Annex 2: Alwan AA, Modell B. Community Control of Genetic and Congenital Disorders. EMRO Technical Publications Series 24. World Health Organisation Regional Office for the Eastern Mediterranean. 1997. (218 pp).

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