**Title:**

**Birth prevalence of Congenital Talipes Equinovarus in Low and Middle Income Countries: A Systematic Review and Meta-analysis**

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Abstract

**Background:** Congenital talipes equinovarus (CTEV), or clubfoot, is a structural malformation that develops early in gestation. Birth prevalence of clubfoot is reported to vary both between and within low and middle-income countries (LMICs) and this information is needed in order to plan treatment services. This systematic review aims to understand the birth prevalence of clubfoot in LMIC settings.

**Methods:** Six databases were searched for studies that reported birth prevalence of clubfoot in LMICs. Results were screened and assessed for eligibility using pre-defined criteria. Data on birth prevalence were extracted and weighted pooled estimates were calculated for different regions. Wilcoxon rank-sum test was used to examine changes in birth prevalence over time. Included studies were appraised for their methodological quality, and a narrative synthesis of findings was conducted.

**Results:** Forty-eight studies provided data from 13,962,989 children in 20 countries over 55 years (1960 – 2015). The pooled estimate for clubfoot birth prevalence in LMICs within the Africa region is 1.11 (0.96, 1.26); in the Americas 1.74 (1.69,1.80); in South East Asia (excluding India) 1.21 (0.73, 1.68); in India 1.19 (0.96, 1.42); in Turkey (Europe Region) 2.03 (1.54, 2.53); in Eastern Mediterranean region 1.19 (0.98, 1.40); in West Pacific (excludes China) 0.94 (0.64, 1.24) and in China 0.51 (0.50, 0.53).

**Conclusion:** Birth prevalence of clubfoot varies between 0.51 and 2.03/1,000 live births in LMICs. A standardised approach to the study of the epidemiology of clubfoot is required to better understand the variations of clubfoot birth prevalence and identify possible risk factors.

# Background

Congenital anomalies, also known as birth defects, are one of the leading causes of disability in children (1). Clubfoot is one of the most common congenital deformities that causes mobility impairment (2). The structure and position of the foot are affected and untreated clubfoot results in pain and reduced mobility, which potentially leads to participation restrictions and activity limitation (3).

Clubfoot forms in the early weeks of gestational development, and this may be part of specific syndromes or secondary to neurologic or systemic disease. However the majority of cases occur in isolation and are termed “idiopathic” (4), the cause of which are not fully understood (5). Genetic factors have been implied (6, 7) while environmental factors, for example seasonal variation and intrauterine immobility, have been reported in some studies (5, 8). Associations with ethnicity are not clear. Other risk factors that have been reported are male gender (9-11), maternal smoking (10-15) and maternal diabetes (10, 13). However, the underlying pathogenesis for these factors remains a matter of scientific debate. A multifactorial etiologic model that involves both environmental and genetic factors is likely (8).

Epidemiological studies consistently report higher birth prevalence (16) of idiopathic clubfoot in males and in first-born children (17). The condition is bilateral in half of the cases (18). Typically a small set of statistics are routinely cited for birth prevalence of clubfoot with reports of 0.39 per 1,000 births in Chinese populations, 1.1 per 1000 in Caucasian and 6.8 per 1,000 in Polynesian populations (19). Overall, it is estimated that 80% of children born with clubfoot each year live in low and middle income countries (LMICs) (18).

Accurate collection of data on population birth rate and prevalence of birth defects is essential to plan, initiate and develop healthcare services. The aim of this study was to conduct a systematic literature review to estimate the birth prevalence of clubfoot in different World Health Organisation (WHO) regions, in order to inform planning of services and programme management in LMICs.

# Methods

The systematic review was planned, conducted and reported according to established MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (20) (Web Appendix 1). A systematic literature search was conducted in January 2016 for peer-reviewed articles that presented original research findings on the birth prevalence of clubfoot in LMIC settings.

*Search Strategy*

EMBASE, Medline, Global Health, LLACS, Africa Wide Information and the Cumulative Index to Nursing, Allied Health Literature (CINAHL) were examined for studies published between 1960 and December 2015 to capture 55 years of data. It was hypothesised that studies that reported on several congenital birth deformities may not include clubfoot in the search terms. Consequently, in order to capture all relevant studies, a search was carried out using both birth defects and clubfoot terms, with LMIC keywords. Boolean, truncation and proximity operators were used to construct and combine searches for the key concepts as required for individual databases and an example is available as Web Appendix 2.

The articles returned by the literature search were screened by one reviewer (TS) first by title and then by abstract. Ten percent of the abstracts were reviewed by a second reviewer (HK) to check for agreement. The full text was obtained for any paper that was included at abstract screening.

Studies of all languages were included and translated as required. The reference list of all included studies were examined for further relevant studies. All full texts were reviewed independently by two reviewers (TS and either AF, CL or HK) and differences were agreed by discussion.

The search strategy is presented in Figure 1.

Search with clubfoot and birth defect terms in LMICs (January 2016) (n= 2377)

Identification

 542 duplicates removed

1835 Titles screened for eligibility

1608 records excluded:

* 1178 no mention of congenital foot disorder
* 374 no mention of incidence, prevalence or distribution
* 56 not original research

Screening

227 Abstracts screened for eligibility

104 records excluded:

59 no mention of clubfoot

45 no mention of incidence, prevalence or distribution

123 Full-text articles assessed for eligibility

51 records excluded:

23 not primary research

5 not in LMIC

10 report prevalence only

13 report risk factors

Eligibility

72 Full texts report incidence

24 full text excluded:

16 retrospective data review design and unclear that all children were screened for clubfoot

2 full texts included duplicate data published

6 definitions did not allow CTEV incidence calculation

48 studies included after quality assessment

Included

**Figure 1 Search strategy with PRISM flow diagram**

*Study selection*

Congenital talipes equinovarus was defined as a rigid deformity where the foot is fixed in a plantarflexed, supinated and adducted position. Studies were eligible if they met the following criteria: (1) original research that included congenital talipes equinovarus, (2) results reported, or allowed calculation of, birth prevalence of clubfoot, (3) all children were screened for clubfoot; and (3) undertaken in a LMIC as defined by the World Bank country classification 2015. Exclusion criteria comprised: (1) full text unavailable, (2) unclear that all children were screened for clubfoot (e.g. large reviews of medical records), (3) unclear source population that prevented clear definition of the population denominator, or (4) duplicate reports from the same study.

*Data extraction and analysis*

Data were extracted from articles that met inclusion criteria according to The Centre for Reviews and Dissemination (CRD) guidelines(21). The following data were extracted:

(1) General study information, including title, author and year of publication

(2) Study design

(3) Study setting and dates conducted

(4) Population characteristics

(5) Primary research outcome, including case definitions and results

All extracted values were examined by the second reviewer to ensure accuracy. Differences between the reviewers were discussed and a consensus was reached on all papers. One author was contacted for further information.

Data reporting per 1,000 births were assumed to be live births unless it was stated that stillbirths were included. Birth prevalence rates were calculated per 1,000 live births with 95% confidence intervals (Wilson score intervals), on the basis of the binomial distribution using Stata 14.0 (StataCorp LP, College Station, Texas), from the reported study population and the number of babies identified with clubfoot. It was decided *a priori* that the populations of China and India would be analysed independently of their WHO region due to their large population size. Tests for heterogeneity were performed. Weighted summary measures were estimated for the six WHO regions, India and China with a fixed effect model (22) in the meta-analysis. The relative weight that each study contributed was defined by the sample size of the study. The overall effect estimate is therefore a weighted combination of the studies that contribute to it. Summary measures were graphed with forest plots.

As the timeframe for the included studies is wide, an analysis was undertaken to identify if the birth prevalence of clubfoot was different in the oldest estimates. A two-sample Wilcoxon rank-sum (Mann-Whitney) test was used to compare the birth prevalence in the time periods 1960 – 1985 and 1986 – 2015, consisting of twenty-five and thirty years respectively.

Cases born per million total population per year were estimated according to regional clubfoot birth prevalence and crude birth rate per 1,000 people. The Global Health Observatory data repository provided estimates of crude birth rate.

# Results

1,835 studies were retrieved for assessment (Figure 1). Of these, 72 studies reported on birth prevalence of clubfoot and provided data from 25 countries (Web Appendix 3). 24 full texts were excluded, of which 15 papers were retrospective data collection and analysis and it was unclear if all children were screened (Web Appendix 4 contains details on the studies excluded). Therefore, forty-eight studies were selected for inclusion and provided data from 13,962,989 children in 20 countries.

Table 1 summarises the characteristics of the studies eligible for inclusion. All the studies drew cases from a hospital setting. Eight of 37 studies (21.6%) that used a prospective design with physical examination were undertaken in more than one hospital (23-30). Nine studies used a large database review in settings where there was systematic screening for clubfoot (31-39), one study analysed data from a single hospital defects monitoring system (40) and one study used a cluster sample survey (41). 13 papers (27%) were from the South East Asia region, with 11 papers in the region published from India. The West Pacific region consisted primarily of research undertaken in China and used large database reviews. Turkey was the only LMIC represented in Europe.

The pooled estimates for clubfoot birth prevalence for Africa (1.11 [0.96, 1.26]), South East Asia (1.21 [0.73, 1.68]), India (1.19 [0.96, 1.42]), and the Eastern Mediterranean Region (1.19 [0.98, 1.40]) are similar. The pooled estimate for clubfoot birth prevalence in LMICs within the Americas Region is 1.74 (1.69,1.80); in Turkey (Europe Region) 2.03 (1.54, 2.53) and in West Pacific (excluding China) 0.94 (0.64, 1.24). The birth prevalence is lowest in China at 0.51 (0.50, 0.53).

Analysis of the birth prevalence of clubfoot reported in two date ranges (1960 – 1985 and 1986 – 2015) demonstrated no evidence of a difference over time (p=0.56).

**Table 1 Studies of CTEV Birth prevalence included in Systematic Review, 1960 – 2015\***

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Reference | Country | Study Time | Period of study | Population | Setting | Method of case ascertainment | Population N | Clubfoot N | Birth prevalence per 1000 | Wilson (score) | Clubfoot definition |
| Primary Author | Year |
| **Africa** |
| Simpkiss (42) | 1961 | Uganda | 1956 - 1957 | 10 months | live births | 1 hospital | Clinical evaluation by medical student or midwife | 1, 927 | 1 | 0.52 | 0.09 - 2.93 | musculoskeletal system: talipes equinovarus |
| Lesi (43) | 1969 | Nigeria | 1966 - 1967 | 1 year | Births | 1 maternity hospital | Clinical evaluation within 12 hours of birth by primary author and assistant nurse | 16, 720 | 19 | 1.14 | 0.73 - 1.77 | congenital defects found according to system' bony: talipes |
| Pompe van Meerdervoort (44) | 1976 | South Africa | Not defined | about 3 years' | Live births | 1 hospital | Physical examination day after delivery by paediatric/ orthopaedic registrar. Positive confirmation by clubfoot specialist.  | 10,000 | 35 | 3.50 | 2.52 - 4.86 | Excluded spina bifida, arthrogryposis and CP. Noted CTEV: fixed deformity |
| Delport (45) | 1995 | South Africa | 1986 - 1989 | 3 years | Live births | 1 urban academic hospital | Clinical evaluation within 24 hours of birth by paediatrician or medical officer | 17, 351 | 8 | 0.46 | 0.23 - 0.91 | Talipes equinovarus ICD 9 code 75450 |
| Venter (46) | 1995 | South Africa | 1989 - 1992 | 3 years 6 months | Live births | 1 rural hospital | Physical examination by trained nurse  | 7,617 | 19 | 2.49 | 1.60 - 3.89 | musculoskeletal system: talipes equinovarus |
| Mkandawire (47) | 2004 | Malawi | 2000-2002 | 22 months | Births | 1 hospital | Physical examination of all neonates, when and by whom not outlined | 16, 877 | 34 | 2.01 | 1.44 - 2.81 | definition of idiopathic and secondary |
| Mathias (48) | 2010 | Uganda | 2006 - 2007 | 20 months | Live Births | 8 regional hospitals | Physical examination by delivery room staff and confirmation by clubfoot specialist | 110,336 | 130 | 1.18 | 0.99 - 1.40 | Clear definition of clubfoot: positional, idiopathic or syndromic |
| Orimolade (49) | 2014 | Nigeria | 2014 | 6 months | Live births | 1 tertiary hospital | Physical examination after delivery | 1,551 | 5 | 3.22 | 1.38 - 7.52 | Idiopathic clubfoot variety |
| **Americas** |  |
| Monteleone-Neto and Castilla (30) | 1994 | Brazil | 1982 - 1985 | 4 years | Live births | 3 maternity hospitals in Cubatao  | Physical examination, prospective collection  | 10,218 | 21 | 2.06 | 1.34 – 3.14 | ECLAMC definition Limb deformity: "talipes” |
| Lopez – Camelo (37) | 1996 | Latin America | 1967 - 1989 | 32 years | Births | Large database 24 geographic regions of Latin America | ECLAMC (Latin American Collaborative Study of Congenital Malformations) | 2,159,065 | 3,769 | 1.75 | 1.69 – 1.80 | pes equinus' |
| Guardiola (39) | 2009 | Brazil  | 2000 - 2005 | 5 years | Births | Large database | ECLAMC | 26, 588 | 41 | 1.54 | 1.14 – 2.09 | Clubfoot as defined by ECLAMC |
| Pachajoa (40) | 2011 | Columbia | 2004 - 2008 | 4 years 7 months | Births | Review of data monitoring system in 1 tertiary care  | hospital birth defects monitoring system | 32, 995 | 58 | 1.76 | 1.36 -2.27 | ICD-10 and ECLAMC version 2002 |
| **South East Asia** |
| Simatupang (50) | 1977 | Indonesia | 1970 - 1975 | 5 years | live births | 1 hospital [General RSUPP Medan] | Prospective, physical examination 'soon after birth' | 17,241 | 19 | 1.10 | 0.71 - 1.72 | talipes' |
| Kalra (51) | 1984 | India | not specified | 14 months | births | 1 obstetric department,[SN medical college, Agra] | physical examination within 28 hours of birth, no description of by whom | 2, 720 | 4 | 1.47 | 0.57 - 3.78 | "musculoskeletal system" talipes equinovarus' |
| Bahadur (52) | 1986 | India | 1980 - 1984 | 5 years | live births | not stated | Examination of infants after birth | 13, 321 | 21 | 1.58 | 1.03 - 2.41 | congenital talipes equinovarus' |
| Chaturvdei (53) | 1989 | India | 1986-1986 | 12 months | births | 1 hospital | physical examination within 48hours of birth | 3, 014 | 3 | 1.00 | 0.34 - 2.92 | musculoskeletal talipes |
| Choudhury (54) | 1989 | India | 1986 - 1987 | 12 months | Live births | 1 hospital, West Bengal | Physical examination | 10, 415 | 4 | 0.43 | 0.15 – 1.99 | No numerator for clubfoot. Noted as talipes.  |
| Agarwal (55) | 1991 | India | 1981 - 1984 | 2 years 6 months | single births | 1 hospital | Physical examination during the early neonatal period | 9,405 | 30 | 3.19 | 2.24 - 4.55 | Talipes equinovarus |
| Singh (56) | 1991 | India | 1984 - 1987 | 4 years | live births | 1 hospital, level II care to neonates | Physical examination by neonatal consultant | 7, 015 | 32 | 4.56 | 3.23 - 6.43 | CTEV |
| Taksande (57) | 2010 | India | 2005 - 2007 | 2 years 7 months | live births | 1 rural medical college hospital  | Physical review by consultant at time of birth | 9, 194 | 11 | 1.20 | 0.67 - 2.14 | musculoskeletal system:'talipes' |
| Chotigavanichaya (58) | 2012 | Thailand | 2009 | 4 months | births | 1 hospital  | Clinical examination within 24hours | 3,396 | 8 | 2.36 | 1.19 – 4.73 | idiopathic clubfoot used Dimeglio classification |
| Pujari (59) | 2012 | India | Not defined | 1 year | live births | 1 hospital | physical examination within 24-48hours of birth | 4,280 | 6 | 1.40 | 0.64 – 3.06 | CTEV |
| Agrawal (60) | 2014 | India | 2010 - 2011 | 1 year | births >28 weeks | 1 tertiary care hospital  | Physical examination for musculoskeletal defects within 24hours of delivery | 7, 268 | 15 | 2.06 | 1.25 - 3.40 | talipes equinovarus' noted these were not positional |
| Sachdeva (61) | 2014 | India | 2010 | 4 months | births | 1 government hospital | Clinical evaluation by paediatrician soon after birth. Data collection by 30 trained residents | 2, 862 | 8 | 2.80 | 1.42 - 5.51 | talipes equinovarus |
| Baruah (62) | 2015 | India | 2010 - 2013 | 2 years 9 months | live births | 1 hospital  | Physical examination within 24hours | 17, 052 | 23 | 1.35 | 0.89 - 2.02 | ICD-10 classification |
| **Europe** |  |
| Say (63) | 1973 | Turkey | 1969 | 10 months | live births >28 weeks | 1 hospital | Physical examination within 48 hours by specialists | 9,947 | 22 | 2.20 | 1.46 - 3.35 | musculoskeletal system 'clubfoot'  |
| Tuncbilek (26) | 1999 | Turkey | 1993 - 1994 | 12 months | births >20 weeks | 22 university hospitals  | Physical examination by paediatrician | 21, 907 | 43 | 1.96 | 1.46 - 2.64 | ICD-10 was used 'pes equinus' |
| **Eastern Mediterranean** |
| Akhtar (64) | 1970 | Pakistan | 1965 – 1968 | 3 years | live births | Obstetric department in 1 hospital | Obstetric dept. reported data, reviewed by research team | 3,570 | 3 | 0.84 | 0.29 - 2.47 | specific report of CTEV in Pakistan |
| Khrouf (65) | 1986 | Tunisia | 1983-1984 | 9 months | Births | 1 teaching hospital | Clinical evaluation within 24hours of birth by paediatric staff | 10, 000 | 26 | 2.6 | 1.77 - 3.81 | musculoskeletal system, 'club foot' with additional deformities |
| Bittar (66) | 1998 | Lebanon | 1991 – 1993 | 2 years 6 months | live births | 1 hospital | Physical examination within 24 hours by senior resident and pre-discharge examination by paediatrician | 3,865 | 7 | 1.81 | 0.88 - 3.73 | musculoskeletal 'equinovarus' |
| Ali (67) | 2008 | Iran | 2003 – 2006 | 2 years 8 months | live births | 1 hospital | physical examination after birth by primary author | 4,660 | 15 | 3.22 | 1.95 - 5.30 | musculoskeletal 'clubfoot' |
| Karbasi (23) | 2009 | Iran | 2003 – 2004 | 8 months | live births | All maternity hospitals in Yadz | Physical examination by Paediatrician | 4, 800 | 19 | 3.96 | 2.54 - 6.17 | ICD-10  |
| Delshad (24) | 2009 | Iran | 2005 – 2007 | 2 years | all births | Maternity wards in 6 government hospitals | Physical examination by paediatrician | 61,112 | 62 | 1.01 | 0.79 - 1.30 | ICD-10 |
| Al-Ani (68) | 2012 | Iraq | 2010 – 2011 | 1 year | births | 1 tertiary hospital | Examined by neonatal specialists | 5,864 | 8 | 1.36 | 0.69 - 2.69 | specified difference idiopathic and secondary. |
| Golalipour (69) | 2013 | Iran | 2007 | 1 year | live births | 1 hospital | Physical examination by a paediatrician | 6, 204 | 5 | 0.81 | 0.34 - 1.89 | ICD-10 classification 'musculoskeletal system clubfoot' |
| El Koumi (70) | 2013 | Egypt | 2011 | 1 year | live births | 1 hospital | Physical examination within 24hours | 2,517 | 6 | 2.38 | 1.09 - 5.19 | ICD-10 'musculoskeletal minor talipes' |
| **West Pacific** |
| Emanuel (25) | 1972 | China | 1965 - 1968 | 3 years | Singleton live and stillborn >28weeks | 6 hospitals in Taipei | Examination by 1 of 4 study physicians, 2 public health nurses follow up | 25, 549 | 19 | 0.74 | 0.48 - 1.16 | ICD 1965 version, "no reducible defect" |
| Boo (71) | 1990 | Malaysia | 1988 | 4 months | births | 1 maternity hospital, | Routine examination by Doctor, referred to research team  | 8, 369 | 4 | 0.48 | 0.19 - 1.23 | calculated structural clubfoot |
| Thong (27) | 2005 | Malaysia | 2002 - 2003 | 14 months | births | All health centres and hospitals in Kinta district | population-based birth defect register: physical examination by trained nurse | 17, 720 | 23 | 1.30 | 0.87 - 1.95 | ICD-10  |
| Li (31) | 2008 | China | 1997 - 2007 | 10 years | births | Guangdong Province, 21 cities | Hospital based surveillance program | 150, 357  | 152  | 1.01  | 0.86 - 1.18  | ICD-9 and ICD-10 |
| Hoang (28) | 2013 | Viet Nam | 2010 | 1 year | Live births | 127 Commune Health Stations | Physical examination within 24hours of birth | 13,954 | 17 | 1.22 | 0.76 – 1.95 | ICD-10 |
| Li (41) | 2013 | China | 2008 - 2010 | 2 years | live births | 4 counties in Hengyang province | Cluster sampling survey | 52,307 | 50 | 0.96 | 0.73 - 1.26 | clubfoot  |
| Yi L (32) | 2013 | China | 2001 - 2010 | 10 years | births | Large database review | Data from birth defects monitoring programme | 8,273, 382 | 4233 | 0.51 | 0.49 – 0.53 | ICD-10 Q66.0 |
| Yi Q-Y (38) | 2013 | China | 2008 - 2011 | 4 years | births | Birth defects monitoring programme in Dongguan | Prospective collection of birth defects on hospital cards | 556 282 | 537 | 0.97 | 0.89 – 1.05 | Congenital clubfoot |
| Wang (33) | 2014 | China | 2006 - 2013 | 8 years | births | Database review in Haikou | Review birth defects registry forms and perinatal infants quarterly report | 118, 199 | 62 | 0.52 | 0.41 - 0.67 | talipes equinovarus' |
| Wei Hong (34) | 2014 | China | 2011 - 2013 | 3 years | births | Hospital surveillance programme in Zuhai city | Data from monitoring institutions | 87, 059 | 53 | 0.61 | 0.46 - 0.79 | talipes equinovarus' |
| Yang (35) | 2015 | China | 2003 - 2009 | 7 years | births | Database review 26 medical institutions [Longgang district] | review of birth defects surveillance network | 191, 017 | 137 | 0.72  | 0.61 - 0.85 | talipes equinovarus' |
| Xia (36) | 2015 | China | 1997 - 2011 | 15 years | births | Large database 75 hospitals [Henan Province] | Population based congenital anomalies surveillance system | 1,815, 920 | 757 | 0.42 | 0.39 - 0.45 | ICD-10 |

\*Studies are ordered by WHO region and year of publication

A meta-analysis by region was undertaken (Figures 2 – 9). The individual study results are displayed in the first column, identified under the title ‘Study.’ The summary birth prevalence is displayed in the final row with the test for heterogeneity denoted as I^2. (If I2≤25%, studies are regarded as homogeneous). The second column visually displays the study results. The third column is the summary estimate of the birth prevalence of clubfoot, denoted by ES (95%CI) or effect size. This column gives the corresponding numerical results. The vertical line is the pooled estimate of birth prevalence and the x-axis is the value of clubfoot cases per 1,000 live births. The size of the box is directly related to the ‘weighting’ of the study in the meta-analysis and the weight in % in the final column indicates the influence of the study on the overall results. The horizontal lines through the boxes depict the length of the confidence intervals. The diamond in the last row of the graph illustrates the overall result of the meta-analysis. The middle of the diamond sits on the value of the summary birth prevalence and the width of the diamond depicts the width of the overall CI.

**Figure 2 Birth prevalence of CTEV per 1,000 births (Africa Region)**

**Figure 3 Birth prevalence of CTEV per 1,000 births (Region of the Americas)**

**Figure 4 Birth prevalence of CTEV per 1,000 births (South East Asia Region excluding India)**

**Figure 5 Birth prevalence of CTEV per 1,000 births (India)**

**Figure 6 Birth prevalence of CTEV per 1,000 births (Europe Region)**

**Figure 7 Birth prevalence of CTEV per 1,000 births (Eastern Mediterranean Region)**

**Figure 8 Birth prevalence of CTEV per 1,000 births (West Pacific Region excluding China)**

**Figure 9 Birth prevalence of CTEV per 1,000 births (China)**

Based on the evidence since 1960, figures to plan for clubfoot management can be calculated for the eight populations given the birth rate per million population (Table 2).

**Table 2 Projected clubfoot cases born per million total population/year**

|  |  |  |  |
| --- | --- | --- | --- |
| Region | Birth prevalence | Crude Br/1000$ | Clubfoot cases born per million total population/ year |
| Africa | 1.11 (0.96, 1.26) | 38.3 | 43 (37 – 48) |
| Americas | 1.74 (1.69, 1.80) | 17.0 | 30 (29 – 31) |
| SE Asia  | 1.02 (0.76, 1.27) | 19.9 | 20 (15 – 25) |
| Turkey(Europe Region) | 2.03 (1.54, 2.53) | 17.0 | 35 (26 – 43) |
| Eastern Mediterranean | 1.19 (0.98, 1.40) | 26.2 | 31 (26 – 37) |
| India | 1.19 (0.96, 1.42) | 20.4 | 24 (20 – 20) |
| West Pacific  | 0.94 (0.64, 1.24) | 14.7 | 14 (9 – 18) |
| China  | 0.51 (0.50, 0.53) | 13.3 | 7 |

$Accessed WHO data, October 2016. http://apps.who.int/gho/data/view.main.CBDR2040

Population numbers are based on WHO region population birth rates. For planning purposes, regional estimates of birth prevalence should be applied to country specific birth rates.

# Discussion

This review summarises 48 studies of clubfoot birth prevalence from LMIC settings with data from 13,962,989 children in 20 countries. To our knowledge, this is the first systematic review of birth prevalence of clubfoot. The results demonstrate a range in birth prevalence from 0.51 (0.50, 0.53) per 1,000 live births in China to 2.03 (1.54, 2.53) per 1,000 in Turkey. Pooled estimates of birth prevalence rates appear to be similar in Africa, South East Asia, Eastern Mediterranean regions and India. There was no evidence for a difference in clubfoot birth prevalence in LMICs between 1960 -1985 and 1986 – 2015.

The case numbers and denominator population size differ in the individual studies included in the meta-analyses. The birth prevalence of clubfoot in China is strongly influenced by two large outlier studies (32, 36) that decrease the pooled estimate. Both studies were database reviews of data from hospitals that monitored birth defects through physical examination and the data were collated on a congenital anomaly registration form. The authors note it is possible that cases were missed. Alternatively, the data may represent a unique feature of inheritance in the idiopathic clubfoot population of China. Only two papers contribute to the estimates of Turkey and the South East Asia region with combined screened populations of 31,854 and 20,637 children respectively.

*Results compared to other studies*

Many LMICs lack rigorous congenital anomaly surveillance programmes (72) which makes calculation of birth prevalence difficult. Current estimates range from 4 to 12 cases per 1,000 births (73) in LMIC settings. These are likely underestimated due to stigma and exclusion (74) and are also reliant on case definition and robust screening methods.

This analysis suggests some variation in the birth prevalence of clubfoot as previously indicated (75), however the range is not as large as reported by others (19). Except for China, there were similar estimates across the regions.

Current data heterogeneity suggests the resulting variation in clubfoot birth prevalence in LMICs is likely influenced by study design and data collection methods and possibly by region and therefore ethnicity as well. Case definition, the case mix between tertiary and secondary facilities and the training of observers may affect prospective reporting of clubfoot. The true birth prevalence will be affected by risk factors, genetic and/or environmental, most of which are unknown.

*Strengths and limitations*

A strength of this study is the relatively large population denominator in several regions. It includes all categories of structural clubfoot (for example idiopathic or syndromic) as treatment is required in all cases although outcomes may differ. Data were excluded from clinics where it was not clear from the report how many babies were examined and did not have clubfoot, as birth prevalence cannot be calculated without a denominator. This has resulted in the exclusion of some studies (76, 77) that are regularly cited. This review is limited by the quality and representation of the available data from LMICs.

*Implications*

The estimated birth prevalence of clubfoot will be useful for the planning of services and to better estimate areas of need for country programmes. For instance, one equipped clinic in each district of 1 million people will be sufficient to handle clubfoot treatment if the new case load is up to 43 cases of clubfoot each year, as estimated by this review. Screening at birth for clubfoot is important, so that cases can be detected and treated early, when treatment is most effective. Scaling up appropriate services for screening and treatment remain a priority.

Future studies should ensure that a clear case definition and robust screening methods are undertaken to allow comparison of epidemiological data.

# Conclusions

Clubfoot is relatively common and should be detected at birth. There is no evidence for a large variation in birth prevalence between regions or of the folklore about a large Polynesian birth prevalence. Comparison of prevalence figures for congenital malformations reported from different parts of the world requires clear case definition and comparable methods of data collection.

The published data over the last 55 years for clubfoot in LMIC suggests a birth prevalence in the range of 0.5 to 2.0 cases / 1,000 live births, which results in an estimated 7 to 43 cases of clubfoot / year / million population, dependent mainly on birth rate.

The regional figures, for example in sub-Saharan Africa of approximately 43 cases / year / million population provide useful information on planning treatment services for clubfoot in LMIC. A standardised approach to the study of the epidemiology of clubfoot is required to better understand the variations of the birth prevalence of clubfoot and possible risk factors.

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**Web Appendix 1 – MOOSE Checklist [for Meta-analysis Of Observational Studies in Epidemiology]**

**Background**

*Problem definition*

The birth prevalence of clubfoot or congenital talipes equinovarus (CTEV) is reported to vary in the literature due to inconsistent case definition and population denominators.

*Hypothesis statement*

Studies of CTEV in low and middle income countries (LMICs) report different birth prevalence estimates. Studies will be homogenised and the differences in birth prevalence will be examined in terms of WHO country definition and changes in time.

*Study outcomes*

* Birth prevalence of CTEV: Number of cases of congenital talipes equinovarus per 1,000 live births
* Generate a homogenous dataset that will allow for comparisons between LMICs and between the date ranges of 1960 – 1985 and 1986 - 2015.

*Type of exposure or intervention used*

* Geography was assessed using LMICs (World Bank 2005) in the WHO regions: African region, Region of the Americas, South East Asia Region, European Region, Eastern Mediterranean Region and the Western Pacific Region. India and China were estimated individually due to large population size.
* Changes over time were assessed in two time periods: 1960 – 1985 and 1986 – 2015
* The Global Health Observatory data repository provided estimates of regional crude birth rate to allow estimation of cases born per million total population per year.

*Type of study design used*

* Observational studies of CTEV

*Study population*

* All children in the study population were screened for clubfoot
* Clear definition of study population with a reliable estimate of the denominator population.
* If the population was well defined and birth prevalence given without the number of cases outlined, cases were calculated with the given information.

**Reporting of search strategy**

*Qualifications of searchers*

* Tracey Smythe has trained in systematic methods of literature searching as part of her PhD studies at the London School of Hygiene and Tropical Medicine
* Prof Christopher Lavy, Prof Allen Foster and Dr Hannah Kuper have participated in many systematic reviews.

The researchers were guided by:

* Jane Falconer, librarian at LSHTM and Fellow of the Higher Education Academy
* David Macleod, Research Fellow, Department of Medical Statistics

*Search strategy*

* Six medical literature databases searched between January 1960 and January 2016
* The following search terms were used as keywords:

|  |  |
| --- | --- |
| 1 | developing country |
| 2 | developing or less\* developed or under developed or underdeveloped or middle income or low\* income  |
| 3 | underserved or under served or deprived or poor\*) adj (economy or economies).ti,ab.  |
| 4 | developing or less\* developed or under developed or underdeveloped or middle income or low\* income |
| 5 | underserved or under served or deprived or poor\*) adj (countr\* or nation? or population? or world)).ti,ab. |
| 6 |  (low\* adj (gdp or gnp or gross domestic or gross national)).ti,ab. |
| 7 | (low adj3 middle adj3 countr\*).ti,ab. |
| 8 |  (lmic or lmics or third world or lami countr\*).ti,ab. |
| 9 | Name of Country according to World Bank 2015 classification  |
| 10 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 |
| 11 | clubf??t |
| 12 | club-f??t |
| 13 | club ADJ1 f??t |
| 14 | talipes equinovarus |
| 15 | talipes ADJ2 equinovarus |
| 16 | talipes ADJ2 equino-varus |
| 17 | congenital talipes equinovarus |
| 18 | congenital ADJ2 talipes ADJ2 equinovarus  |
| 19 | CTEV |
| 20 | 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 |
| 21 | birth defect or birth malformation or birth abnormality or congenital defect or congenital malformation or congenital abnormality |
| 22 | incidence or occurrence or frequency |
| 23 | 21 and 22 |
| 24 | 20 or 23 |
| 25 | 10 and 25  |

*Effort to include all available studies, including contact with authors*

* The final list of included studies were discussed with experts in the field: Rosalind Owen, Executive Director of the Global Clubfoot Initiative and Nyengo Mkandawire, Professor of Orthopaedics, Malawi
* Studies of all languages were included and translated as required
* Primary authors were contacted for clarification of study period

*Databases and registries searched*

* EMBASE, Medline, Global Health, LLACS, Africa Wide Information and the Cumulative Index to Nursing, Allied Health Literature (CINAHL)

*Use of hand searching*

* The reference list of all included studies were examined for further relevant studies.

*List of citations located and those excluded, including justification*

* See web appendix 4 for full texts that were excluded
* Studies were first excluded by title and then by abstract
* The full text was obtained for any paper that was included at both title and abstract screening
* 72 full texts were read by 2 reviewers and included or excluded according to the criteria listed.

|  |  |
| --- | --- |
| Inclusion Criteria | Exclusion criteria |
| 1. Original research that included congenital talipes equinovarus
 | (1) Full text unavailable |
| 1. Results reported, or allow calculation of, birth prevalence of clubfoot
 | (2) Unclear that all children were screened for clubfoot |
| 1. Undertaken in LMIC as defined by the World Bank country classification 2015
 | (3) Unclear source population that prevents clear definition of the population denominator |
| 1. All children were screened for clubfoot
 | (4)Duplicate reports from the same study |

*Method of addressing articles published in languages other than English*

* Non-English articles were translated for each article obtained

*Method of handling abstracts and unpublished studies*

* Studies published only as abstracts where the case definition and denominator population were not defined were excluded, as were those that were unpublished.

*Description of any contact with authors*

* Four papers required additional information from authors to ascertain their precise study period. One author (Thong 2005) was contacted via the details provided in the published study. The study period was clarified as 7th January 2002 to 28th February 2003.

**Reporting of methods**

*Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested*

* All studies that provide observational epidemiological data on children born with confirmed CTEV
* Studies in LMICs in all WHO regions are included
* The studied period spans 55 years from 1960 to 2015

*Rationale for selecting and coding of data*

* Studies were included and excluded as per the criteria outlined above
* 10% of the abstracts were reviewed for agreement
* All full texts were reviewed independently by 2 reviewers (TS and either HK, CL or AF) and differences agreed by discussion
* Data were extracted according to The Centre for Reviews and Dissemination (CRD) guidelines
* Birth prevalence were recorded per 1,000 live births
* Wilson score confidence intervals were calculated

*Documentation of how data were classified and coded*

* Details are outlined within the methods section of the text

*Assessment of confounding*

* Not applicable with Wilcoxon rank-sum test due to small numbers of studies per region before 1985, two date ranges were assessed globally.

*Assessment of study quality*

* Inclusion/exclusion criteria were strict to ensure adequately defined study boundaries and case ascertainment

*Assessment of heterogeneity*

* Heterogeneity was assessed geographically, and statistically to identify differences between studies

*Description of statistical methods*

* Birth prevalence rates and Wilson score confidence intervals were calculated (using Stata 14.0) and plotted using forest plots
* The pooled estimate of birth prevalence was calculated per WHO region
* Wilcoxon rank sum test was used to examine change in birth prevalence between two time periods

**Reporting of results**

*Graphic of individual summary estimates and pooled estimate*

* Forest plots are drawn to demonstrate birth prevalence and confidence intervals
* A weighted pooled estimate of birth prevalence of clubfoot was calculated according to WHO region

*Table giving descriptive information of all studies included and excluded*

* Table of studies included is available within the body of text
* Web appendix 4 lists all excluded papers with reasons for exclusion

*Indication of statistical uncertainty of findings*

* 95% Wilson score confidence intervals for all calculated birth prevalence are given

**Reporting of discussion**

*Quantification of bias*

* Quantification of bias is not possible with this study design.

*Justification of exclusion*

* Papers were excluded based upon exclusion criteria and justification is outlined within text. Excluded papers and reasons for exclusion are listed in Web Appendix 4.

*Assessment of quality of included studies*

* The inclusion/exclusion criteria maximised the quality of included studies and the uncertainty is illustrated by 95% confidence

**Reporting of conclusions**

*Consideration of alternative explanations for observed results*

* Outlined in the discussion section of the main text

*Generalisation of these conclusions*

* Projected clubfoot cases per million population were estimated

*Guidelines for further research*

* Outlined in the discussion section of the main text

*Disclosure of funding source*

* Tracey Smythe received funding from the Beit Trust and Christian Blind Mission (CBM)

**Web Appendix 2 Search terms for clubfoot and birth defects and LMICs**

|  |  |
| --- | --- |
| 1 | developing country |
| 2 | developing or less\* developed or under developed or underdeveloped or middle income or low\* income  |
| 3 | underserved or under served or deprived or poor\*) adj (economy or economies).ti,ab.  |
| 4 | developing or less\* developed or under developed or underdeveloped or middle income or low\* income |
| 5 | underserved or under served or deprived or poor\*) adj (countr\* or nation? or population? or world)).ti,ab. |
| 6 |  (low\* adj (gdp or gnp or gross domestic or gross national)).ti,ab. |
| 7 | (low adj3 middle adj3 countr\*).ti,ab. |
| 8 |  (lmic or lmics or third world or lami countr\*).ti,ab. |
| 9 | Name of Country according to World Bank 2015 classification  |
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| 11 | clubf??t |
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| 13 | club ADJ1 f??t |
| 14 | talipes equinovarus |
| 15 | talipes ADJ2 equinovarus |
| 16 | talipes ADJ2 equino-varus |
| 17 | congenital talipes equinovarus |
| 18 | congenital ADJ2 talipes ADJ2 equinovarus  |
| 19 | CTEV |
| 20 | 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 |
| 21 | birth defect or birth malformation or birth abnormality or congenital defect or congenital malformation or congenital abnormality |
| 22 | incidence or occurrence or frequency |
| 23 | 21 and 22 |
| 24 | 20 or 23 |
| 25 | 10 and 25  |

**Web Appendix 3 Papers reporting CTEV birth prevalence published by year and WHO region prior to quality assessment**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Years | Total number of Papers | African Region | Region of the Americas | South-East Asia Region | European Region | Eastern Mediterranean Region | Western Pacific Region |
| 1960 - 1969 | 2 | Uganda (1)a, Nigeria (1) |   |  |  |  |  |
| 1970 - 1979 | 6 | South Africa (1) |   | India (1), Indonesia (1), Pakistan (1) | Turkey (1) |  | Taiwan (1) |
| 1980 - 1989 | 9 | South Africa (1),  |  | India (6), Thailand (1) |  | Tunisia (1) |  |
| 1990 - 1999 | 13 | South Africa (2) | Brazil (1), Latin America (2) | India (3), Indonesia (1), Malaysia (1) | Turkey (1) | Lebanon (1), Pakistan (1) |  |
| 2000 - 2009 | 15 | Malawi (2), Nigeria (2), Zimbabwe (1) | Brazil (1) | Malaysia (1)  |  | Iran (4), Libya (1) | China (1), Philippines (1), Papua New Guinea (1) |
| 2010 - 2015 | 26 | Nigeria (3), Uganda (1) | Brazil (1), Columbia (2),  | India (6), Thailand (1) |  | Egypt (1) , Iran (2), Iraq (1) | China (8), Viet Nam (1)  |

a Number of published papers

**Web Appendix 4 Full text excluded studies**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Primary Author and Reference** | **Year** | **Country** | **Study design** | **Data source** | **Time** | **Population** | **Population N** | **Clubfoot N** | **Birth prevalence /1000** | **Reason** |
| Dash Sharma (78) | 1970 | India | Data review  | Records of birth | 3 years | live births | 5,554 | 2 | 0.36 | Retrospective data review, unclear if all children screened |
| Kromberg and Jenkins (76) | 1982 | South Africa | Data review | Data from register of births in the nursery ward, paediatric ward and mortuary records | 2 years | births | 29, 633 | 46 | 1.55 | Retrospective data review, unclear if all children screened |
| Choudhury (79) | 1984 | India | Data review | Hospital records of birth registers | 4 years | births | 21, 016 | 6 | 0.29 | Retrospective data review, unclear if all children screened |
| Limpaphayom (80)  | 1985 | Thailand | Data review | Medical records | 2 years | births | not specified | 104 | 1.30 | No specified population |
| Roychoudhury (81) | 1988 | India | Data review | Maternity records | not specified | births | 72, 617 | not specified | varied from 0.02 to 0.11 | Retrospective data review, unclear if all children screened |
| Castilla (82) | 1990 | Latin America | large database review | ECLAMC (Latin American Collaborative Study of Congenital Malformations) data | 4 years | births | Tropical: 287,165 | tropical: 442 | tropical: 1.54 | ECLAMC data used in Lopez - Camelo paper  |
| Non tropical: 582, 585 | non: 615 | non: 1.06 |
|
| Masloman (83) | 1991 | Indonesia | Data review | Medical records of department of child health | 5 years | births | 13, 354 | 11 | 0.82 | Retrospective data review, unclear if all children screened |
| Bhat (84) | 1998 | India | Prospective, physical examination | Physical examination within 24 hours | 3 years 3 months | births | 12, 797 | 40 (36 live, 4 still) | 3.13 | All foot deformities included |
| Najmi (85) | 1998 | Pakistan | Prospective, physical examination | Physical examination by Paediatrician | 2 years 8 months | live births | 11,148 | 2 TEV and 2 TE | 0.18 | Unclear definition |
| Singh (86) | 2000 | Libya | Data review | Maternal records, NICU registry and stillborn / death certificates | 1 year | Births | 16, 186 | 2: clubfoot or 4 : talipes | 0.37 | Retrospective data review, unclear if all children screened |
| Madzivire (87) | 2002 | Zimbabwe | Data review | Children attending clubfoot clinic, with population under 4 years | 3 years | Hospital catchment area | 96,942 | 82 | 0.85 | Retrospective data review, unclear if all children screened |
| Mkandawire (88) | 2002 | Malawi | Prospective physical examination | Research nurse identified and photographed | 13 months | Live births | 9,838 | 11 | 1.12 | Data included in paper published in 2004 |
| Padilla (89) | 2003 | Philippines | Large database | Birth defects registry | 12 months | Births | 191, 567 | 73 | 0.38 | Includes all congenital deformities of the feet |
| Abdi-Rad (90) | 2008 | Iran | Data review | Chart review | 4 years 6 months | Births | 14, 121 | 27 | 1.90 | Retrospective data review, unclear if all children screened |
| Ekanem (91) | 2008 | Nigeria | Data review | Data extracted from birth registries | 23 years | Birth registry in 2 states of Nigeria | 127, 929 | 31 | 0.24 | Retrospective data review, unclear if all children screened |
| Culverwell (77)  | 2009 | Papua New Guinea | Data review | Clubfoot clinic notes  | 2 years | Live births and children presenting to hospital | 11, 215 (based on 2000 census data)  | 60 | 2.67 | Retrospective data review, unclear if all children screened |
| Bakare (92) | 2009 | Nigeria | Prospective, physical examination | Physical examination | 1 year | Live births | 624 | 5 | 8.00 | All foot deformities |
| Zarante (93) | 2010 | Columbia | Large database | ECLAMC | 6 years 9 months | Births | 52, 744 | 132 | 2.50 | Foot deformities include calcaneovalgus |
| Ukoha (94) | 2011 | Nigeria | Data review | Hospital records | 6 years | Children attending hospital between 1 day and 2 years | 12,464 | 43 | 3.00 | Data review for children attending hospital - not birth prevalence |
| Ekanem (95)  | 2011 | Nigeria | Data review  | Maternity records | 13 years | Births | 19,572 | 8 | 0.41 | Retrospective data review, unclear if all children screened |
| Zhu (96)  | 2012 | China | Data review | Data of neonates with congenital malformations was reviewed | 1 year | Live births | 6,725 |  2 |  0.30 | Retrospective data review |
| Vakilian (97) | 2013 | Iran | Data review | Review of maternal files  | 7 years | Live births | 20,751 | not specified  | 2.98  | Retrospective data review, unclear if all children screened |
| Nhoncanse (98) | 2014 | Brazil  | Data review | Review of birth certificates | 5 years | Live births | 12,199 | 4 | 0.32 | Retrospective data review, unclear if all children screened |
| Ghorpade (99) | 2015 | India | Data review | Medical chart review  | 10 years | Live births | 10, 674 | 60 | 5.62 | Retrospective data review, unclear if all children screened |

a ordered by year

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