Epidemiology of Robin sequence in the UK and Ireland: an active surveillance study

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ABSTRACT

Background

Birth prevalence of Robin sequence (RS) is commonly reported as 1 case per 8000–14 000 live births. These estimates are based on single-source case ascertainment and may miss infants who did not require hospital admission or those without overt upper airway obstruction at birth.

Objectives

To identify the true birth prevalence of RS with cleft palate in the UK and Ireland from a population-based birth cohort with high case ascertainment.

Methods

Active surveillance of RS with cleft palate was carried out in the UK/Ireland using dual sources of case ascertainment: British Paediatric Surveillance Unit (BPSU) reporting card and nationally commissioned cleft services. Clinical data were collected from notifying clinicians at two time points.

Results

173 live-born infants met the surveillance case definition, giving a birth prevalence of 1 case per 5250 live births (19.1 per 100 000 (95% CI 16.2 to 21.9)), and 1:2690 in Scotland. 47% had non-isolated RS, with Stickler syndrome the most common genetic diagnosis (12% RS cases). Birth prevalence derived from the combined data sources was significantly higher than from BPSU surveillance alone.

Conclusions

Birth prevalence of RS in the UK/ Ireland derived from active surveillance is higher than reported by epidemiological studies from several other countries, and from UK-based anomaly registries, but consistent with published retrospective data from Scotland. Dual case ascertainment sources enabled identification of cases with mild or late-onset airway obstruction that were managed without hospital admission. Studies of aetiology and equivalent well-designed epidemiological studies from other populations are needed to investigate the identified geographical variability in birth prevalence.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Global birth prevalence of Robin sequence (RS) is reported as 1:8000–1:14 000 live births, which may be an underestimation. In the UK/ Ireland, regional birth prevalence estimates from anomaly registries are widely variable.
- Higher birth prevalence has been described in Scotland.

WHAT THIS STUDY ADDS

- Active surveillance with multiple data sources indicates that birth prevalence of RS in the UK/ Ireland is 1:5250 live births. This is higher than reported by congenital anomaly registries and studies using single data sources. A significantly higher prevalence in Scotland (1:2690) was again found.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This accurate birth prevalence estimate can be used to plan appropriate medical services for infants with RS in the UK/Ireland.

INTRODUCTION

Robin sequence (RS) is a congenital disorder characterised by micrognathia and glossoptosis, resulting in upper airway obstruction (UAO).[1] Cleft palate is a common additional feature, present in 83%–92% of cases.[2–4] Feeding difficulties result from a combination of factors including abnormal tongue position, oropharyngeal dysfunction, cleft palate and respiratory distress.[1 5] The findings of RS may occur in isolation, or in association with additional congenital anomalies or an underlying genetic syndrome (non-isolated RS).

RS has a spectrum of clinical severity; some infants tolerate oral feeding and have mild UAO that can be alleviated with positioning techniques, whereas others are unable to safely feed orally and have severe airway obstruction. This can result in protracted hospital admissions with a need for tube feeding and/or invasive airway support measures.[6] In some cases, UAO symptoms may not be recognised until several weeks after birth or can present subclinically with growth faltering.[3 7]

Birth prevalence of RS has historically been reported as 1 case per 8000–14 000 live births based on studies from the UK and Europe.[3 8 9] However, these studies were limited to infants who required hospital admission in the first year of life or with manifest respiratory distress in the neonatal period, which may have underestimated birth prevalence. More recently, studies from the USA, Netherlands and Scotland have reported a higher birth prevalence of 1 in 2685– 5600 live births.[4 6 10]

The aim of this study was to ascertain the true birth prevalence of RS in the UK and Ireland, including infants with mild or subclinical UAO who may have been missed by previous epidemiological studies.

METHODS

We conducted an active surveillance study of RS through the British Paediatric Surveillance Unit (BPSU) over a 13-month period (January 2016 to January 2017). The BPSU sends a monthly rare diseases reporting card to consultant paediatricians and neonatologists across the UK/Ireland which consistently achieves a response rate of over 90%.11 Clinicians were asked to report any infant born in the UK/Ireland during the surveillance period with each of the following characteristics: (1) micrognathia, retrognathia or glossoptosis; (2) cleft palate; and (3) resulting clinical compromise (signs of UAO, feeding difficulties or growth faltering) (box 1).

This case definition was chosen by the study team, in collaboration with the BPSU scientific committee, in the absence of a consensus definition for RS in clinical practice or within published research at the time of study development. An inter- national consensus definition was published after study onset which differed from the case definition applied in this study by considering cleft palate as a common additional feature of RS, but not mandatory for diagnosis.[1]

Dual reporting sources were used to maximise case ascertainment. Cleft care in the UK/Ireland is nationally commissioned and babies with cleft palate are referred to one of 12 regional cleft services (RCS). Each RCS participated by either reporting cases prospectively via a monthly electronic survey, or reporting the total number of RS cases registered during the surveillance period and submitting data for cases that were not detected by BPSU surveillance.

Reporting clinicians and RCS were asked to complete two surveys: an initial survey at the time of case notification and a follow-up survey when each child was at least 12 months old. Surveys collected the following clinical data: demographic information including ethnicity (physician assigned according to 2001 census ethnicity coding),[12] antenatal history, clinical presentation, additional congenital anomalies, type and duration of airway and feeding management, results of genetic testing and other specialist assessments and serial growth parameters. Dupli- cate reports were identified and combined into a single entry using a limited data set of patient identifiable data. RS genetic classification (isolated or non-isolated RS) was assigned by two authors (MFAW+RLK) based on review of the complete data set.

UAO severity was assigned according to the level of intervention delivered: UAO managed with prone or side-lying positioning was classified as mild, management with non-surgical interventions as moderate and with surgical airway intervention as severe UAO.

Analyses were performed using the R language and environment for statistical computing V.4.0.5 and SPSS V.27.0 (IBM).

RESULTS

Case reporting

Three hundred and six notifications were received: 198 via the BPSU and 108 from RCS. The survey response rate from BPSU surveillance was 85%. After removing erroneous reports and duplicates, 173 confirmed cases were included in the study (figure 1), of which 48% (n=83) had been missed by BPSU surveillance and identified by RCS. Median age at first survey completion was 16 weeks, and follow-up survey completion was 2.0 years. Ninety-five per cent of respondents completed both surveys.

Birth prevalence

There were 907 572 live births in the UK/Ireland during the surveillance period,14–17 giving a birth prevalence for RS of 1 case per 5250 live births (19.1 per 100 000 (95% CI 16.2 to 21.9)). This varied between countries; highest in Scotland (1:2690) and lowest in England and Wales (1:5790) (figure 2). Birth preva- lence derived from BPSU surveillance alone was 1:10 080 (9.9 per 100 000 (95% CI 7.9 to 12.0)) (table 1).

Patient characteristics

Patient characteristics are described in table 2. Ethnicity was reported in 167/173 infants: 84% (n=141) were from white ethnic groups and 10% (n=17) were of Asian ethnicity. One child was from a black ethnic group. Based on 2016 births in England and Wales, RS birth prevalence among white infants was 1:5320 (18.8 per 100 000 (95% CI 15.0 to 22.6)), Asian (Indian, Pakistani, Bangladeshi) infants 1:4680 (21.4 per 100 000 (95% CI 9.8 to 33.0)) and black infants 1:29 568 (3.4 per 100 000 (95% CI 0 to 10.0)). Birth statistics by ethnicity were not available for other countries. There were no differences in clinical characteristics by country of birth (online supplemental table 1).

RS classification

Forty-seven per cent (n=81) of infants had non-isolated RS, of which 65% (n=53) had an RS-associated syndrome or genetic abnormality. The most common syndromes were Stickler syndrome, constituting 12% of RS cases (n=20), and campomelic dysplasia (n=3). Ten per cent (n=18) had an RS-as- sociated chromosomal abnormality (table 3, online supplemental table 2). The remaining 35% (n=28) had multiple congenital anomalies without a unifying genetic diagnosis, most commonly affecting the cardiovascular (43%, n=12) or musculoskeletal (29%, n=8) systems (online supplemental figure 1). Seventy-nine per cent of infants (n=136) had undergone genetic testing or clinical geneticist evaluation, and 72% (n=124) underwent ophthalmology assessment.

Diagnosis and initial management

RS was suspected antenatally in 15% of cases (n=24/160), most often based on micrognathia on ultrasound (n=13). Cleft palate and/or glossoptosis were only identified antenatally in two cases (online supplemental table 3). Median age at RS diagnosis was 1 day (range: 1–14 days), and 97% were diagnosed prior to hospital or maternity unit discharge. Ninety-three per cent (n=160/172) were admitted to hospital, either a neonatal or paediatric unit, for a median of 21 days (IQR 28 (12–40) days).

Ninety-four per cent of infants (n=159/170) had feeding difficulties requiring nasogastric tube feeding in the newborn period, and 52% (n=41/79) developed growth faltering in the first 3 months of life. Ninety-one per cent of infants (n=157) had signs of UAO, giving a birth prevalence for RS with UAO of 1:5780 live births (17.3 per 100 000 (95% CI 14.6 to 20.0)). Over two-thirds of infants received an airway intervention: 58% (n=100) had moderate UAO which was managed non-surgically and 11% (n=19) had severe UAO requiring tracheostomy insertion (data are summarised in table 2). Infants reported via the BPSU were significantly more likely to be admitted to hospital (p=0.029) and require airway intervention (p=0.027) than those identified **by RCS alone.**

DISCUSSION

Key findings

Within the UK/Ireland, the birth prevalence of RS according to active surveillance is 1:5250 live births, with substantial geographical variation. Birth prevalence in Scotland was 1:2690 (37.1 per 100 000 (95% CI 21.6 to 52.7)), which closely resembles the birth prevalence of 1:2685 live births (37.2 per 100 000 (95% CI 30.1 to 44.4)) determined previously by our group in an East of Scotland cohort.[6] As the same surveillance case definition was used in all participating countries this likely represents a true geographical difference in birth prevalence. Furthermore, UAO was present in all Scottish cases, and the proportion of infants with severe UAO requiring surgical intervention was highest in Scotland, suggesting that the higher birth prevalence was not due to a lower threshold for RS diagnosis in borderline or mild cases. The aetiology of RS is not fully understood and is likely to be multifactorial, including genetic disposition and exposure to environmental risk factors during embryogenesis. Proposed exposures include methadone[6 18–20] and cigarette smoking.[21] Geographical differences in birth prevalence may relate to variation in

genetic profiles and environmental exposures, or a 'latitude gradient' as has been identified for several other diseases.[22–24] Studies of aetiology are required to investigate these hypotheses.

Birth prevalence of RS is frequently cited as 1:8500–14 000 live births based on national studies from Germany (2011–2013) and Denmark (1990–1999).[3 8] The study by Maas and Poets was conducted through the German Paediatric Surveillance Unit which has a similar methodology and surveillance card response rate to the BPSU.[25] However, as notifications were made by hospital-based paediatricians without alternative sources of ascertainment, infants who were not admitted to hospital would have been missed. In contrast, our study included community paediatricians and used RCS as an alternative reporting source. In the UK/Ireland, early identification of cleft palate and evaluation by a specialised cleft clinician within 24 hours of birth is a standard of care,[26] therefore the likelihood of all cases of RS with cleft palate being known to RCS is high. The use of nationally commissioned cleft services as a second reporting source enabled us to identify children managed in outpatient settings who were not detected by BPSU surveillance and increased the birth prevalence estimate from 1:10 080 to 1:5250.

Printzlau and Andersen[8] retrospectively identified cases of RS from the Danish cleft registry, to which reporting of cleft cases is legally mandated. Their diagnostic criteria included evidence of respiratory distress at clinical review in the first few days of life. However, UAO in RS may not be diagnosed at birth and can progressively worsen over several weeks, or can be present intermittently, for example, when feeding or during supine sleep. Additionally, UAO can be subclinical, presenting with growth faltering which resolves after an airway intervention is introduced.[3 5 7 27] Epidemiological studies that exclude cases without overt UAO in the neonatal period may conse- quently underestimate birth prevalence.[8 9] In view of this, our case definition included growth faltering as an alternative to overt UAO. The German surveillance study applied a similar case definition with the same rationale.[3]

Data from reporting to congenital anomaly registries in the UK/ Ireland also indicate a lower birth prevalence of RS than identified by our study. The EUROCAT (European network of population-based registries for the epidemiological surveillance of congenital anomalies) network described the epidemiology of RS derived from 29 European congenital anomaly registries over a 20-year period (1998–2017).[2] Birth prevalence from the eight registries within the UK/Ireland was 1:8950 births, ranging from 1:5380 (Wales) to 1:14 930 (Wessex, England). Scotland was not, however, represented in the EUROCAT data set. The Cleft Registry and Audit Network, the national clinical audit database of the Royal College of Surgeons of England,[28] identified the birth prevalence of RS in England, Wales and Northern Ireland in 2016 as 1:9270 live births based on voluntary registrations requiring caregiver consent (personal correspondence). However, some congenital anomaly registries may underestimate disease prevalence, particularly when registration is voluntary, caregiver consent is required or passive surveillance is used. There is an additional risk of under-reporting if diagnosis of the congenital condition requires specialist experience, as can be the case with RS. Furthermore, data entered for registered cases may be incomplete or inaccurate.[29] A medical chart review of patients within the Dutch national cleft registry found that over half of children with a clinical diagnosis of RS had been miscategorised as having an isolated cleft palate.[30] In a subsequent study, 31% of the Dutch cleft palate population had RS based on chart review, compared with 21% according to registry data, which increased the national RS birth prevalence estimate from 1:8600 to 1:5600 live births.[4]

Differences in inclusion criteria, for example, the inclusion of stillbirths by EUROCAT, are also likely to have contributed to disparate birth prevalence estimates between sources.

Ethnicity

We found a similar birth prevalence of RS in white and Asian infants, which contrasts with a reported higher birth prevalence among non-Hispanic white infants in California, USA.[31] Our finding of a lower birth prevalence among black infants should be interpreted cautiously given that black ethnic groups constitute a small proportion of the population of UK/Ireland, but two large studies spanning multiple US states have similarly described a lower prevalence for both RS and all types of orofacial clefts among infants from black ethnic backgrounds.[10 32]

These apparent variations in birth prevalence between ethnic groups may relate to differences in prevalence of RS-associated genetic mutations. Racial differences in craniofacial characteristics, including predisposition to structural narrowing of the upper airway in some ethnic groups, are another potential contributory factor.[33 34] Further research is needed to confirm whether ethnic differences in prevalence exist and to better understand the causes of such differences.

RS classification

In our population, 47% of individuals had non-isolated RS, most commonly due to Stickler syndrome. This is consistent with a systematic review by Gomez-Ospina and Bernstein, which identified 50% of RS cases as non-isolated (n=1385 RS cases, n=16 studies).[35] A second systematic review (n=324 cases, n=39 studies) reported 63% of cases as non-isolated, but this proportion may have been overestimated by the inclusion of case reports and case series focusing on specific syndromic diagnoses.[36] In contrast, EUROCAT reported a predominance of isolated RS (68%), which may reflect under-recognition of associated anomalies by registry-based studies.[2]

One explanation for differences in the reported frequency of non-isolated RS between studies is variability in thresholds for genetic evaluation. In centres where genetic testing is less commonly performed, non-isolated RS may be misdiagnosed as isolated RS. To date, only Basart and colleagues have published a series of consecutive patients with RS (n=191) with complete genetic evaluation.[37] Non-isolated RS was diagnosed in 62% of cases, with Stickler syndrome accounting for 14%, chromosomal abnormalities 9% and 22q11.2 deletion 1.2% of RS cases. Within our cohort, over three-quarters of infants were referred to a clinical geneticist or underwent genetic testing, and 72% had an ophthalmology assessment to screen for Stickler syndrome, making it unlikely that RS-associated genetic diagnoses were significantly underdiagnosed.

Strengths

This study has several strengths. BPSU surveillance has a large reporting base of over 3500 paediatricians and achieved high reporting card and survey response rates (94% and 85%, respectively) during this study.[11] We anticipate near complete case ascertainment, resulting in accurate estimation of birth prevalence, as this study involved active surveillance and used dual reporting sources with contribution from nationally commissioned cleft services to which all

babies with cleft palate are referred. We attempted to minimise potential differences in diagnostic thresholds by use of a precise surveillance case definition which could be easily applied based on routine clinical assessment by the various types of healthcare practitioner contributing to the study.

Limitations

A challenge when conducting epidemiological studies of RS is variability in its diagnostic criteria. Our surveillance case definition differed slightly from the consensus report published after the commencement of our study, which regards micrognathia, glossoptosis and UAO as mandatory for diagnosis with cleft palate as a common additional feature.[1] However, even when including only infants with overt UAO (therefore aligning our cohort more closely to the consensus definition), our birth prevalence estimate remained higher than any previously published regional reports from the UK/Ireland[2 9] or any other national surveillance studies.[3 8] The inclusion of cases of RS without cleft palate would only increase our birth prevalence estimate further.

Data were collected from contemporaneous routine medical records, and patients were not recalled for clinical assessment, resulting in some instances of missing data. As additional clinical assessments and investigations could not be carried out within this study, UAO severity and RS genetic classification were not measured in a standardised way. Instead, a pragmatic approach was taken whereby UAO severity was classified according to the type of airway intervention used, and genetic classification was assigned according to available clinical information and investigation results. This approach may have resulted in some cases of misclassification.

Although our study design was prospective, some data were submitted retrospectively by cleft teams in cases missed by BPSU reporting, which introduces a potential for recall bias.

We attempted to achieve complete case ascertainment using multiple reporting sources, but we may have missed a small number of cases, for example, early neonatal deaths prior to cleft palate or RS diagnosis.

CONCLUSIONS

Birth prevalence of RS in the UK/Ireland estimated by this active surveillance study was 1:5250 live births, which is higher than reported by registry-based studies using routine monitoring data over the same period. Scotland had a particularly high prevalence rate, consistent with previously published data.

The high birth prevalence seen in our population might reflect more complete case ascertainment than attained by previous epidemiological studies and existing registries. This study highlights the importance of active surveillance, use of alternative reporting sources that enable identification of cases managed in either inpatient or outpatient settings and inclusion of cases with subclinical or late diagnosed UAO.

Comparative studies with robust prevalence data from other countries are needed to further investigate the variations in prevalence based on geography and ethnicity identified by this study, which may ultimately increase our understanding of the aetiology of RS. Future studies in

this field should aim to include cases of RS without cleft palate given that this patient group is under-represented in current published research.

REFERENCES

1. Breugem CC, Evans KN, Poets CF, et al. Best practices for the diagnosis and evaluation of infants with Robin sequence: a clinical consensus report. JAMA Pediatr 2016;170:894–902.
2. Santoro M, Coi A, Barišić I, et al. Epidemiology of Pierre-Robin sequence in Europe: a population-based EUROCAT study. Paediatr Perinat Epidemiol 2021;35:530–9.
3. Maas C, Poets CF. Initial treatment and early weight gain of children with Robin sequence in Germany: a prospective Epidemiological study. Arch Dis Child Fetal Neonatal Ed 2014;99:F491–4.
4. Paes EC, van Nunen DPF, Basart H, et al. Birth prevalence of Robin sequence in the Netherlands from 2000-2010: a retrospective population-based study in a large dutch cohort and review of the literature. Am J Med Genet 2015;167:1972–82.
5. Miller CK. Feeding issues and interventions in infants and children with clefts and Craniofacial syndromes. Semin Speech Lang 2011;32:115–26.
6. Wright M, Mehendale F, Urquhart DS. Epidemiology of Robin sequence with cleft palate in the east of Scotland between 2004 and 2013. Pediatr Pulmonol 2018;53:1040–5.
7. Wilson AC, Moore DJ, Moore MH, et al. Late presentation of upper airway obstruction in Pierre Robin sequence. Arch Dis Child 2000;83:435–8.
8. Printzlau A, Andersen M. Pierre Robin sequence in Denmark: a retrospective population-based Epidemiological study. Cleft Palate Craniofac J 2004;41:47–52.
9. Bush PG, Williams AJ. Incidence of the Robin Anomalad (Pierre Robin syndrome). Br J Plast Surg 1983;36:434–7.
10. Scott AR, Mader NS. Regional variations in the presentation and surgical management of Pierre Robin sequence. Laryngoscope 2014;124:2818–25.
11. British Paediatric Surveillance Unit. BPSU annual report 2016-2017. London, UK, 2017. Available: https://www.rcpch.ac.uk/sites/default/files/2018-06/bpsu_annualreport1617_final3_0.pdf
12. UK Government. List of ethnic groups: 2001 census. n.d. Available: https://www. ethnicity-facts-figures.service.gov.uk/style-guide/ethnic-groups
13. National Guideline Alliance. Faltering growth - recognition and management. National Institute for health and care excellence: guidelines. London, UK, 2017.
14. Central Statistics Office. Vital statistics yearly summary. 2017. Available: https://www.cso.ie/en/releasesandpublications/ep/p-vsys/vitalstatisticsyearlysummary2016
15. Office for National Statistics. Births in England and Wales: 2016. 2017. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthsummarytablesenglandandwales/2016
16. Northern Ireland Statistics and Research Agency. Monthly births 2022 (updated monthly). n.d. Available: https://www.nisra.gov.uk/publications/monthly-births

17. Vital events reference tables 2016. 2017. Available: https://webarchive.nrscotland.gov.uk/web/20210314060407/https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/general-publications/vital-events-reference-tables/2016
18. Cleary BJ, Donnelly JM, Strawbridge JD, et al. Methadone and perinatal outcomes: a retrospective cohort study. Am J Obstet Gynecol 2011;204:139.
19. Cleary B, Loane M, Addor M-C, et al. Methadone, Pierre Robin sequence and other congenital anomalies: case-control study. Arch Dis Child Fetal Neonatal Ed 2020;105:151–7.
20. Weaver KN, Sullivan BR, Balow SA, et al. Robin sequence without cleft palate: genetic diagnoses and management implications. Am J Med Genet A 2022;188:160–77.
21. Honein MA, Rasmussen SA, Reefhuis J, et al. Maternal smoking and environmental tobacco smoke exposure and the risk of orofacial clefts. Epidemiology 2007;18:226–33.
22. Simpson S, Wang W, Otahal P, et al. Latitude continues to be significantly associated with the prevalence of multiple sclerosis: an updated meta-analysis. J Neurol Neurosurg Psychiatry 2019;90:1193–200.
23. Webb GJ, Ryan RP, Marshall TP, et al. The epidemiology of UK autoimmune liver disease varies with geographic latitude. Clin Gastroenterol Hepatol 2021;19:2587–96.
24. French J, Simpson-Yap S, van der Mei I, et al. Identification of a latitude gradient in the prevalence of primary biliary cholangitis. Clin Transl Gastroenterol 2021;12:e00357.
25. International Network of Paediatric Surveillance Units. German Paediatric surveillance unit (ESPED). n.d. Available: https://www.inopsu.com/members/map-view/german- unit
26. Bannister P. Management of infants born with a cleft lip and palate. Part 1. Infant 2008;4:5–8.
27. Smith JD. Treatment of airway obstruction in Pierre Robin syndrome. A modified lip- tongue adhesion. Arch Otolaryngol 1981;107:419–21.
28. The Cleft Registry and Audit Network. About us: Royal college of Surgeons of England. 2022. Available: https://www.crane-database.org.uk/about/
29. Kozelj V. Epidemiology of orofacial clefts in Slovenia, 1973-1993: comparison of the incidence in six European countries. J Craniomaxillofac Surg 1996;24:378–82.
30. Rozendaal AM, Luijsterburg AJM, Ongkosuwito EM, et al. Delayed diagnosis and Underreporting of congenital anomalies associated with oral clefts in the Netherlands: a national validation study. J Plast Reconstr Aesthet Surg 2012;65:780–90.
31. Tolarova MM, Cervenka J. Classification and birth prevalence of orofacial clefts. Am J Med Genet 1998;75:126–37.
32. Genisca AE, Frías JL, Broussard CS, et al. Orofacial clefts in the National birth defects prevention study, 1997-2004. Am J Med Genet A 2009;149A:1149–58.

33. Lam B, Ip MSM, Tench E, et al. Craniofacial profile in Asian and white subjects with obstructive sleep apnoea. Thorax 2005;60:504–10.

34. Oh E, Ahn SJ, Sonnesen L. Ethnic differences in Craniofacial and upper spine morphology in children with Skeletal class II malocclusion. Angle Orthod 2018;88:283–91.

35. Gomez-Ospina N, Bernstein JA. Clinical, cytogenetic, and molecular outcomes in a series of 66 patients with Pierre Robin sequence and literature review: 22Q11.2 deletion is less common than other Chromosomal anomalies. Am J Med Genet 2016;170:870–80.

36. Varadarajan S, Balaji TM, Raj AT, et al. Genetic mutations associated with Pierre Robin syndrome/sequence: a systematic review. Mol Syndromol 2021;12:69–86.

37. Basart H, Paes EC, Maas SM, et al. Etiology and pathogenesis of Robin sequence in a large dutch cohort. Am J Med Genet A 2015;167A:1983–92.

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Contributors

MFAW conceptualised and designed the study, designed the data collection instruments, collected the data, conducted the data analysis, drafted the initial manuscript, and acts as guarantor for the study. FVM and SJ contributed to study design and revised the manuscript to provide key intellectual content. MC-B conducted and supervised the data analysis and reviewed and revised the manuscript. RLK supervised the data analysis and interpretation, provided methodological expertise and reviewed and revised the manuscript. DSU conceptualised and designed the study, supervised the data collection and analysis and reviewed and revised the manuscript to provide key intellectual content.

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Competing interests

None declared.

Ethics approval

This study involves human participants and was approved by the South-East Scotland Research Ethics Committee (15/SS/0049) and supported by the Health Research Authority Confidentiality Advisory Group (15/CAG/0141) to collect data without individual participant consent.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

TABLES AND FIGURES

Box 1 Surveillance case definition of Robin sequence (RS)

The presence of each of the following clinical findings in a live- born infant who was born in the British Isles (UK or Ireland) during the surveillance period:

- Micrognathia, retrognathia or glossoptosis.
- Cleft palate.
- Evidence of resulting clinical compromise (≥1 of the following):
    - Signs of upper airway obstruction (UAO).
    - Feeding difficulties.
    - Growth faltering (loss of >10% birth weight within the first 2 weeks of life or crossing down two centile lines on a standardised growth chart).

Table 1 RS birth prevalence by country, sex and reporting source

Country	RS cases	Live births	Cases/100,000 LB (95% CI)	Birth prevalence per 1 case	Male (95% CI)	Female (95% CI)	BPSU only (95% CI)
England & Wales	130	752,508	17.3 (14.3 – 20.2)	1:5,789	17.6 (13.3 – 22.0)	19.8 (15.0 – 24.5)	9.7 (7.5 – 11.9)
Scotland	22	59,223	37.1 (21.6 – 52.7)	1:2,692	42.5 (18.5 – 66.5)	38.1 (14.5 – 61.7)	13.5 (4.15 – 22.9)
Northern Ireland	6	26,321	22.8 (4.6 – 41.0)	1:4,387	8.0 (0 – 23.8)	42.9 (5.3 – 80.5)	6.6 (0 – 24.2)
Republic of Ireland	15	69,520	21.6 (10.7 – 32.5)	1:4,635	24.4 (7.5 – 41.4)	22.4 (5.8 – 39.1)	8.6 (1.7 – 15.5)
All countries of UK/ROI	173	907,572	19.1 (16.2 – 21.9)	1:5,246	19.5 (15.3 – 23.7)	21.8 (17.3 – 26.3)	9.9 (7.9 – 12.0)

RS = Robin sequence; ROI = Republic of Ireland; LB = live births; CI = confidence interval; BPSU = British Paediatric Surveillance Unit

Table 2 Clinical characteristics of children with RS

Characteristic	Data available (*n*, %)	*n*	% RS cases
Gestational age	173 (100%)		
Term		151	87%
Preterm (<37 weeks)		22	13%
Sex	173 (100%)		
Female		89	51%
Male		84	49%
RS classification	172 (99%)		
Isolated		91	53%
Non-isolated		81	47%
Ethnicity	167 (97%)		
White		141	84%
Asian		17	10%
Mixed/other		9	5%
Country of birth	173 (100%)		
England & Wales		130	75%
Scotland		22	13%
Northern Ireland		6	3%
Ireland		15	9%
Hospital admission	172 (99%)		
Admitted		160	93%
Not admitted		12	7%
UAO severity	173 (100%)		
Nil		16	9%
Mild		38	22%
Moderate		100	58%
Severe		19	11%
Nasogastric tube feeding	170 (98%)	159	94%
Growth faltering aged < 3 months	79 (46%)	41	52%
Characteristic	**Data available (*n*, %)**	**Median**	**IQR**
Gestational age, weeks	173 (100%)	39	2 (38 – 40)
Birth weight, grams	171 (99%)	3200	800 (2810 – 3610)
Hospital LOS, days	155/160 (90%)	21	28 (12 – 40)

LOS = length of stay; NGT = nasogastric tube; RS = Robin sequence; UAO = upper airway obstruction

Table 3 Genetic diagnoses in cases of non-isolated RS (n=54)

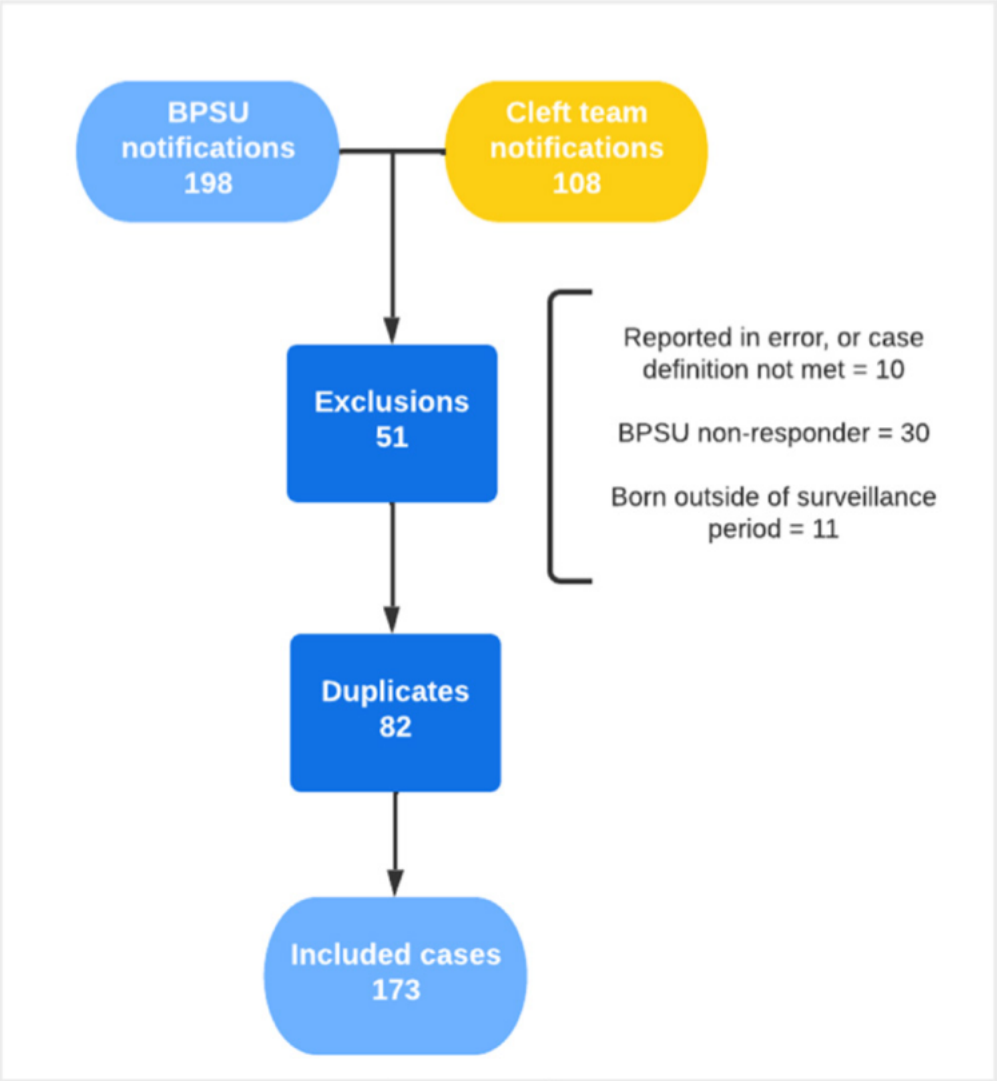
Diagnosis	Number	% RS cases (n=172/173)
Stickler syndrome	20	12%
Chromosomal (seen supplementary table 2)	18	10%
Acampomelic campomelic dysplasia	3	2%
Congenital disorder of glycosylation-PGM1	1	<1%
Sotos syndrome	1	<1%
Distal arthrogryposis syndrome	1	<1%
Patau syndrome	1	<1%
Acrofacial dysostosis	1	<1%
Russell-Silver syndrome	1	<1%
Blepharophymosis syndrome	1	<1%
CHARGE syndrome†	1	<1%
Wolf-Hirschhorn syndrome	1	<1%
Branchio-otic syndrome	1	<1%
Joubert syndrome	1	<1%
Robinow syndrome	1	<1%
Fetal alcohol syndrome	1	<1%
Smith Lemli Opitz syndrome	1	<1%

* One infant with Stickler syndrome had additional congenital anomalies

† Coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness

RS = Robin sequence

Figure 1 Data flow diagram of Robin sequence (RS) case notifications.



BPSU = British Paediatric Surveillance Unit.

Figure 2 Birth prevalence of Robin sequence (RS) by country of UK/Ireland.