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ORIGINAL ARTICLE

Finnish nationwide controlled register study found increased inpatient infections in children with 22q11.2 deletion syndrome

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Abstract

Aim: Studies on treating infections in children with 22q11.2 deletion syndrome (22q11.2DS) have been limited. We characterised inpatient infections and outpatient antibiotic treatment.

Methods: Children born during 2005–2018 were eligible for this national Finnish retrospective register-based study. We recruited 98 children (54% male) with DiGeorge or velocardiofacial syndrome. The 980 matched controls had a benign murmur diagnosed before 1 year of age. The cumulative incidence of infections and antibiotic prescriptions and total prescriptions were measured.

Results: The median age for 22q11.2DS diagnoses was under 1 year of age (range 0–14 years), with a median follow-up time of 9 years for diagnoses and 11 years for prescriptions. Children with 22q11.2DS had significantly higher hospitalisation rates than the controls for any infection (68.1% vs. 30.5%), gastroenteritis (16.8% vs. 4.0%), pneumonia (23.4% vs. 4.3%), severe bacterial infections, excluding pneumonia or pyelonephritis (15.0% vs. 4.1%) and viral wheezing (23.2% vs. 9.1%). Outpatient antibiotic prescriptions were similar, but the children with 22q11.2DS received them earlier than the controls, with a hazard ratio of 3.29 for ages 0–5 years and 1.84 for the entire follow-up.

Conclusion: Children with 22q11.2DS had significantly more infections requiring hospitalisation than controls without the syndrome.

KEYWORDS
antibiotics, DiGeorge syndrome, infection rates, morbidity, velocardiofacial syndrome

1 | INTRODUCTION

22q11.2 deletion syndrome (22q11.2DS) is the most common microdeletion syndrome in humans.[1,2] The principal clinical components of the syndrome are heart defects, structural and functional pharyngeal derangements, hypoparathyroidism, thymic hypoplasia with variable immunodeficiency and neuropsychiatric issues.[3] Children with 22q11.2DS are known to be prone to sinopulmonary infections. This is partly due to anatomical anomalies and partly due to dysfunctional T-lymphocyte function.[4] There have been

Abbreviations: 22q11.2DS, 22q11.2 deletion syndrome; CI, confidence interval; HR, hazard ratio; ICD-10, International Classification of Diseases, Tenth Revision.

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rare reports of infants with typical congenital defects having total athymia. These manifested as potentially life-threatening immunodeficiency that resembled severe combined immunodeficiency.[4,5] Preventive treatment for infections in patients with 22q11.2DS have varied. Some patients were treated with intravenous immunoglobulin replacement therapy or prophylactic antibiotics, but most did not receive either of these interventions.[4,6]

There have been few, if any, publications on antibiotic treatment for infections in children with 22q11.2DS and the literature on inpatient-treated infections has also been lacking. Studies have tended to just focus on the prevalence, without any comparisons to children hospitalised without the syndrome or the timing of the hospitalisations.

The aim of this study was to characterise the infectious morbidity of children with 22q11.2DS, by comparing diagnoses of infections during inpatient treatment to other admissions that reflected the general paediatric population. We also reviewed outpatient antibiotic prescriptions, to further clarify infectious morbidity in these groups.

Key Notes

- Studies on treating children with 22q11.2 deletion syndrome have been limited and this prompted a retrospective nationwide register study.
- Finnish children who were diagnosed with DiGeorge syndrome or velocardiofacial syndrome had significantly more infections that required hospitalisation than matched controls without 22q11.2 deletion syndrome.
- Both groups received a similar number of outpatient antibiotic prescriptions, but children with 22q11.2 deletion syndrome tended to receive these at an earlier age.

2 | METHODS

This retrospective population-based register study focused on children born in Finland from 1 January 2005 to 31 December 2018. Follow-up started at birth and ended on 31 December 2018. Prescription data were available up to the end of 2020, but the children were only followed up until the end of the year when they turned 16 years of age. This was to ensure that the data represented childhood morbidity. The Finnish Care Register was used to identify the study population and gather the relevant data.[7] Data from this Register, and prescription data, were obtained from Findata (permission number THL/164/14.02.00/2021). International Classification of Diseases, Tenth Revision (ICD-10) codes were as used to identify study participants. Children with either ICD-10 code D82.1 for DiGeorge syndrome or Q87.06 for velocardiofacial syndrome were classified as having been diagnosed with 22q11.2DS. Individuals with potential confounding diagnoses (Table S1) were excluded to ensure that the focus of this study was on 22q11.2DS. The matched control group comprised children diagnosed with benign murmurs (ICD-10 code R01.0) before the 1 year of age, who did not have 22q11.2DS or confounding diagnoses. Relevant diagnoses of inpatient episodes were reviewed by three members of the research team (SW, LK and JL). They reviewed the complete list of diagnoses for the entire study population and identified all clinically meaningful diagnosis codes for infectious illnesses. These codes were then grouped into specific categories for analysis. Neonatal infections in Category P00–P96 were excluded. Individual patient assessments and medical charts were not available. The categories are defined in Table S2. Differences between the study groups were analysed using the chi-square test or Wilcoxon rank sum test, as appropriate. Patients with 22q11.2DS were matched with the controls using a ratio of 1:10. The nearest neighbour algorithm was used, with sex and year of birth as propensity variables. The outcomes were studied based on cumulative incidences, using Cox regression and maximum likelihood estimates, stratified by matching. Cause-specific modelling was applied. The results are presented as means, medians, percentages or hazard ratios (HRs) with a 95% confidence interval (CI) or standard deviation (SD). Statistical significance was set at $p < 0.05$. SAS version 9.4 (SAS Institute Inc., North Caroline, USA) and R version 4.3.0 (R Foundation, Vienna, Austria) were used for the statistical analyses.

The Finnish Care Register is maintained by the country's National Institute for Health and Welfare. Every inpatient episode in the Finnish public sector is recorded, and each episode must have at least one diagnosis recorded to justify inpatient treatment. These diagnoses are encoded using the ICD-10 system. Prescription data were available from the Reimbursement for Prescription Medicine Register, which is maintained by the Social Insurance Institution of Finland and managed by Statistics Finland. This register includes every prescribed medication in Finland and the prescription information is encoded according to Anatomical Therapeutic Chemical codes. These data include the date of the prescription, and what medication was prescribed, but information on dosing and indications for treatment are not available from this register.[8]

We were only able to recruit individuals from these registers if an ICD-10 code had been recorded. Using the entire paediatric population as a control group was not technically feasible with the available registers. That is why the benign murmur (ICD-10 code R01.0) was selected as an ideal criterion for recruiting children into the control group. Its notably high prevalence during infancy enabled us to create an age-matched and sex-matched control group. In Finland, infants with a murmur are routinely examined by paediatric cardiologists and the R01.0 code is primarily assigned to patients without structural heart defects. As a result, this approach produced a random sample that approximated the general paediatric population, effectively serving as a surrogate for using population-level data as a control.

The general characteristics of the study population were described in our previous study.[9] This cohort comprised 98 children (54% male)

with 22q11.2DS. Information on ethnicity was unavailable. The median age at diagnosis was under 1 year (range 0–14 years). The incidence was calculated as 1.17 per 10 000 live births, which equated to one in every 8547 live births. This cohort predominantly comprised children with the significant congenital structural anomalies that indicate the more severe forms of 22q11.2DS.

When we measured the cumulative incidence, we only recorded the first infectious event for each patient in each category. This approach was chosen because the Finnish Care Register did do not differentiate between multiple codes that may have represented a single illness episode or separate episodes. However, using the first event provided a reasonable surrogate for representing morbidity across different infectious disease categories. Using the timing of the first event was valuable, as it showed the onset of infectious morbidity in each category.

As this was a retrospective register study, we were not legally required to obtain approval from the hospital's ethical review board or informed consent. The participants' parents were not contacted. The data used in this study are available from Findata and the personal data were processed in line with data protection regulations.

3 | RESULTS

The study groups comprised 98 children with 22q11.2DS and 980 controls. The cumulative incidences of inpatient treatment with at least one specific infectious diagnosis are presented in Table 1. Children with 22q11.2DS were significantly more likely than the control group to have at least one inpatient treatment due to any infectious diagnosis. The cumulative incidences were 68.1% and

TABLE 1 Cumulative incidences of infections in patients with 22q11.2 deletion syndrome and matched controls hospitalised during follow-up.

Outcome	22q11.2DS *n* = 98 (%)	Controls *n* = 980 (%)	Hazard ratio (95% CI)	*p* Value
Any infection	68.1	30.5	3.07 (2.42–3.90)	<0.0001
Gastroenteritis	16.8	4.0	3.34 (1.98–5.63)	<0.0001
Local bacterial infections	35.3	10.9	3.52 (2.53–4.90)	<0.0001
Pneumonia	23.4	4.3	6.81 (4.19–11.05)	<0.0001
Pyelonephritis	3.2	2.8	1.14 (0.36–3.60)	0.829
Severe bacterial infections, excluding pneumonia and pyelonephritis	15.0	4.1	6.57 (3.72–11.58)	<0.0001
Viral wheezing illness	23.2	9.1	2.63 (1.73–4.00)	<0.0001

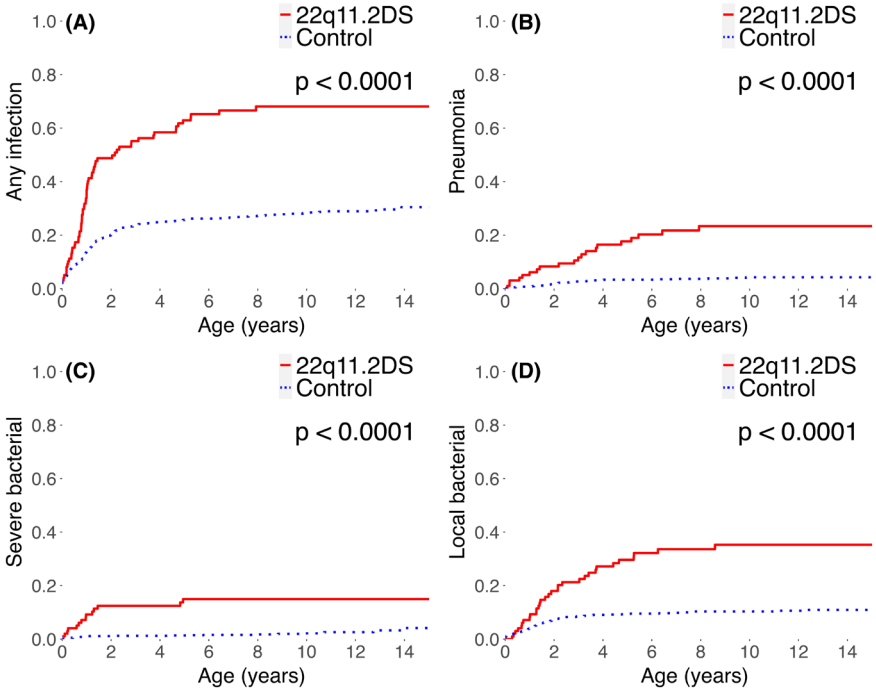

FIGURE 1 Cumulative incidences of first inpatient episodes in the 98 children with 22q11.2 deletion syndrome and their 980 matched controls, reflecting the timing of the onset of infectious morbidity. Categories are as follows: any infectious diagnosis (A), pneumonia (B), severe infections other than pneumonia or pyelonephritis (C) and local bacterial infections (D). *p* Values refer to the differences in cumulative incidences.

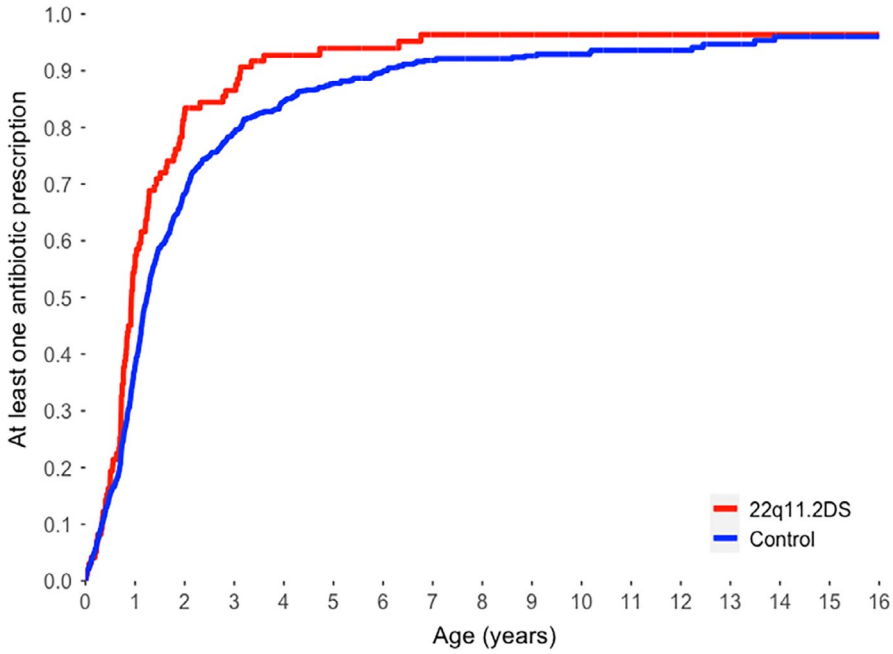

FIGURE 2 Cumulative incidences of first outpatient antibiotic prescriptions in 98 children with 22q11.2 deletion syndrome and their 980 matched controls.

30.5%, respectively ($p < 0.0001$). Local bacterial infections were documented in 35.3% of patients with 22q11.2DS during at least one of their hospital stays, while the control group's rate was 10.9% ($p < 0.0001$). Viral wheezing illnesses were recorded in 23.4% and 9.1% of the 22q11.2DS and control groups, respectively ($p < 0.0001$). Gastroenteritis occurred in 16.8% of the hospitalised patients with 22q11.2DS, but in only 4.0% of the control group ($p < 0.0001$). Patients with 22q11.2DS exhibited a higher occurrence of pneumonia requiring inpatient treatment (23.4%) and all other severe bacterial infections other than pneumonia or pyelonephritis (15.0%), compared to the control children (4.3 and 4.1%, respectively, $p < 0.0001$). The only analysed category that did not significantly differ between the groups was pyelonephritis. The cumulative incidence was 3.2% for the 22q11.2DS group and 2.8% for the control group ($p = 0.829$).

The timing of each child's first inpatient-treated infection was notably earlier in patients with 22q11.2DS across various areas. Most of the patients with this deletion syndrome experienced their first stay involving any infection before the age of 18 months (Figure 1A). The first stays of children with 22q11.2DS who were diagnosed with pneumonia were evenly distributed over the first 8 years of life (Figure 1B). The first ward stays of those with other severe bacterial infections, excluding pneumonia and pyelonephritis, were concentrated within the first 18 months of life (Figure 1C). First-time diagnoses of local bacterial infections during ward stays continued to accumulate in children with 22q11.2DS, up to the age of 6 years (Figure 1D). By contrast, most of the first inpatient stays for infectious diagnoses in the control group had occurred by 2.5 years of age (Figure 1A–D).

The quantitative and qualitative characterisations of the outpatient prescription data are shown in Table S3 and Figure S1, respectively. Both the median and mean follow-up times for the prescription data were 11 years. Almost every child in both groups received at least one outpatient antibiotic prescription during the follow-up period. The cumulative incidence of at least one prescription was 96.4% for the 22q11.2DS group and 96.0% for the control group (Figure 2). There were notable and considerable variations in the data. For example, the highest number of outpatient antibiotic prescriptions for any child was more than 130, while most had fewer than 10 prescriptions during their entire follow-up.

There was no significant difference in the number of yearly outpatient antibiotic prescriptions between the two groups during the entire follow-up period. The median number of antibiotic prescriptions per child, divided by the length of follow-up, was 0.68 for children with 22q11.2DS and 0.55 for the control group ($p = 0.14$). Even when two different age ranges were examined, namely 0–5 and 6–10 years, there were no significant differences in the number of antibiotic prescriptions. The median number of outpatient antibiotic prescriptions per year for children aged 0–5 years was 1.00 for the 22q11.2DS group and 0.80 for the control group ($p = 0.67$). They were 0.25 for both groups aged 6–10 years ($p = 0.28$). However, children with 22q11.2DS were more likely to receive their first outpatient antibiotic prescription earlier than the controls: hazard ratio 3.29 (95% CI 1.12–9.66) for children aged 0–5 years and 1.84 (95% CI 1.13–3.01) for the entire follow-up.

4 | DISCUSSION

This register-based study characterised the infectious morbidity of children diagnosed with 22q11.2DS at an early age. It was conducted by comparing inpatient diagnoses of infection and outpatient antibiotic prescription data for these individuals to matched controls with benign heart murmurs. Children with 22q11.2DS were hospitalised more frequently for various infections than the controls, indicating an increased incidence. Outpatient antibiotics

were prescribed to almost every child in both groups, with no significant difference in the total number of prescriptions. However, children with 22q11.2DS received outpatient antibiotics earlier than the controls as evidenced by statistically significant hazard ratios for ages 0–5 years and the entire follow-up period: 3.29 (95% CI 1.12–9.66) and 1.84 (95% CI 1.13–3.01), respectively. This suggests that there was an earlier onset of antibiotic-treated infections in the 22q11.2DS group.

Previous studies have shown that children with 22q11.2DS frequently experienced infections, with up to 40% hospitalised at least once due to an infection.[10–12] Pneumonia was the most common reason for hospitalisation in these studies, followed by various bacterial and viral infections. We found that 68.1% of our 22q11.2DS group required at least one hospitalisation with any infectious diagnosis and this was even more frequent than the percentage previously reported.[12] However, this may have been partly due to the different statistical methods used.

The data we had available made it impossible to definitively determine whether infectious diagnoses were the primary reasons for admissions. Local bacterial infections, such as acute otitis media, rarely necessitate inpatient treatment and are likely to represent secondary diagnoses. Nevertheless, it is reasonable to presume that many children with serious infectious diagnoses were admitted due to infections. Unfortunately, we were unable to distinguish between nosocomial infections, such as periprocedural infections, and community-acquired infections from the dataset.

We excluded pneumonia and pyelonephritis from the severe bacterial infection category and created separate groups for them. This decision was made because the high frequency of pneumonia in 22q11.2DS has been well-established[13–15] and pyelonephritis tends to be a consequence of structural abnormalities, rather than immunological factors.[16] This enabled us to focus more effectively on the incidence of other severe infections. Up to 15% of children with 22q11.2DS have been reported to experience severe infections that are overshadowed by pneumonia.[6,11] It is crucial to be aware of this possibility, particularly during early childhood.

One notable finding was that there was no difference in admittance due to pyelonephritis. We previously showed that children in the same study population with 22q11.2DS exhibited a higher incidence of congenital urinary tract malformations than the control group.[9] It is possible that the nature of urinary tract anomalies in 22q11.2DS may not have consistently predisposed patients to pyelonephritis.

It is not surprising that antibiotic prescriptions were very common in children with 22q11.2DS. Nearly all of them (96.4%) received at least one outpatient prescription of antibiotic treatment. Although children with 22q11.2DS have been reported to experience infections, such as acute otitis media, more often than the general population,[9] they did not receive more antibiotics. This may have been partly due to the healthcare structure in Finland, where patients with notable syndromes are typically followed up in hospital-based public clinics. Specialist opinions are readily accessible and greater antibiotic stewardship by these healthcare professionals can lead to lower prescription rates than in primary care or private healthcare setting.[17,18]

We did observe a difference in the timing of the first outpatient antibiotic treatment, when it was evaluated using maximum likelihood estimates. Children with 22q11.2DS were 1.8 times more likely to receive a prescription than the control group. This likelihood increased to 3.3 times when we only considered children aged 0–5 years of age. These findings were consistent with our previous finding that individuals with 22q11.2DS tended to experience infections at an earlier age than the control group.[9] We speculate that families with a child with 22q11.2DS diagnosed early in life may be more likely to seek medical attention during an acute illness. This could partly explain why their child received antibiotics at an earlier stage. However, we were unable to verify this interpretation from the register data.

In Finland, antibiotics are commonly prescribed during the first few years of life, primarily for upper respiratory airway infections.[19] Finnish children aged 15 years or less received an estimated average of 6–10 courses of antibiotics in the first two decades of this century.[20] The prevalence of antibiotic prescriptions for children in Finland was estimated to be around 35% in the late 2000s.[19] However, these estimates did not consider the cumulative aspect of prescriptions over the entire period of childhood. This explains the numerical difference with our study's high cumulative incidence of prescriptions in both the 22q11.2DS and control groups.

4.1 | Strengths and limitations

The primary strengths of this study were its nationwide approach and the fact that it provided comprehensive follow-up register data for a rare deletion syndrome over an extended period. However, the register data also had inherent limitations.[21] One key limitation was that it did not provide confirmed results from genetic tests. These investigations are routinely used and readily available in Finland, because they are considered essential for diagnosing genetic diseases. The Finnish Care Register has also been demonstrated to be satisfactory, in terms of the accuracy of primary diagnoses, but subsidiary diagnoses have been regarded as poorly recorded.[22] This restriction was most evident in our cohort, due to the lack of codes for infections associated with surgery.

Our analysis was limited to the first admission for each infection category, due to the challenge of reliably distinguishing true readmissions from these registers. The small number of patients in the 22q11.2DS group meant that we could not reliably stratify the data by major features of the syndrome. In addition, we could not access the patient charts for other factors, such as cluster of differentiation four counts or the use of intravenous immunoglobulin for prophylaxis. Our findings may not be generalisable to milder phenotypes of 22q11.2 deletion syndrome that are often diagnosed later in childhood or even adulthood. This is because this cohort primarily represented children with severe phenotypes, which were

characterised by significant structural anomalies and early diagnosis. The cumulative incidence of infections might have been lower if the entire paediatric population with 22q11.2 deletion syndrome had been analysed, as that would have captured the full incidence of the syndrome.

The nature of the available prescription data also limited our interpretation, because the data did not include the indications for the prescriptions. For example, we could not deduce whether the prescriptions were for treating concurrent infections, or for prophylaxis, and the length of the antibiotic courses were not recorded. In addition, the registers did not include any inpatient prescriptions. We decided not to conduct subgroup analyses by drugs, or their combinations, due to the lack of indication. This was because we did not believe it would have enhanced the characterisation of outpatient infections in this cohort, due to overlapping indications for just about every antibiotic.

5 | CONCLUSION

Infectious morbidity requiring hospitalisation was significantly increased in children with 22q11.2 deletion syndrome, particularly due to pneumonia and other severe bacterial infections. The overall antibiotic prescription rates did not differ from the control group without this syndrome. However, children with 22q11.2DS were more likely to receive antibiotics from outpatient departments at an earlier age. This trend was particularly pronounced during their first 6 years of life and persisted throughout the children's entire follow-up.

AUTHOR CONTRIBUTIONS

Sakari Wahrmann: Conceptualization; data curation; investigation; writing – original draft; writing – review and editing. **Leena Kainulainen:** Data curation; conceptualization; investigation; writing – original draft; writing – review and editing. **Johanna Lempainen:** Project administration; supervision; data curation; investigation; conceptualization; writing – original draft; writing – review and editing. **Ville Kytö:** Conceptualization; investigation; writing – original draft; software; formal analysis; supervision; data curation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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