



Communication

Ocular Chloramphenicol Exposure in Early Childhood in Aotearoa/New Zealand

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Abstract: Background: The paediatric use of ophthalmic chloramphenicol in New Zealand (NZ) is relatively high; however, little more is known about its utilisation, including whether this is equitable. This study aimed to describe chloramphenicol utilisation in NZ children aged five years and under, by patient ethnicity, socioeconomic deprivation, and urban/non-urban domicile. Methods: This analysis included every publicly subsidised chloramphenicol dispensing received from birth to five years of age, for every child born in NZ in 2013. Cumulative proportion of first exposure, dispensing rate per person-year, and seasonality of dispensing were quantified. These were calculated following stratification by ethnicity, socioeconomic deprivation quintile, and urban/non-urban health district. For cumulative proportion of first exposure, odds ratios (OR) were calculated and multivariate logistic regression was performed. For dispensing rate, incidence rate ratios (IRR) were calculated and zero-inflated Poisson regression was performed. Results: Almost one-quarter of NZ children received their first dispensing within the first year of life. By five years of age, 55.2% of children had received their first dispensing. By five years of age, children of Pacific ethnicity, those in the highest deprivation quintile, and in those non-urban health districts had lower odds of receiving chloramphenicol (adjusted OR 0.90, 0.79, and 0.81, respectively, all $p < 0.001$). In contrast, children of Māori ethnicity had higher odds (adjusted OR 1.99, $p < 0.001$). Māori and Pacific ethnicity, and residence in non-urban health districts, were associated with fewer dispensings (adjusted IRR 0.88, 0.75 and 0.87, all $p < 0.001$). In contrast, deprivation quintile was not significantly associated with dispensing rate. Conclusion: Chloramphenicol utilisation is prevalent among NZ children, and utilisation may be lower among children of Pacific ethnicity and those in non-urban areas

Keywords: ophthalmic antibiotics; paediatric drug utilisation; New Zealand

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1. Introduction

The use of ophthalmic antibiotics in the paediatric population is relatively high [1]. Although evidence of substantial clinical benefit is limited, topical antimicrobials are often prescribed in the management of acute bacterial conjunctivitis [2,3]. Acute conjunctivitis is highly prevalent among children, affecting approximately one in eight children annually, with a bacterial aetiology in over 50% of cases [4]. Common causative organisms include *Haemophilus influenzae*, which accounts for around 70% of cases, as well as *Streptococcus pneumoniae* and *Moraxella catarrhalis* [5]. However, evidence supporting usage of topical antimicrobials in acute bacterial conjunctivitis is limited, as most cases are self-limiting and serious complications are rare [2,3]. Antimicrobials are also used inappropriately in non-bacterial cases of conjunctivitis [6].

Antimicrobial use potentially has some adverse consequences. Antimicrobial exposure contributes to the increased development of resistance, and resistant organisms have been found in paediatric ocular isolates [7,8]. With chloramphenicol, although resistance among

ocular isolates is generally low, a few studies have reported high rates of resistance [9]. Topical antimicrobial exposure may also disrupt the paediatric microbiome at the ocular surface [10], and an altered microbiome has been reported in some ocular surface disorders [11]. With chloramphenicol, although there is no strong evidence linking topical use with haematotoxicity, topical chloramphenicol is not in use in the United States, due to concerns around this rare adverse effect being linked to *systemic* administration [12]. Topical chloramphenicol is widely used in many other countries, including the United Kingdom, Australia, and Aotearoa/New Zealand (NZ) [1,3].

Little is known about the paediatric utilisation of ocular antibiotics across NZ. As such, this study aimed to describe the utilisation of ocular chloramphenicol in the first five years of life, and to quantify differences in utilisation between population subgroups. This analysis focused on chloramphenicol, as it is by far the most commonly used ocular antibiotic across NZ [13].

2. Results

This analysis included 62,712 dispensings for 31,703 children. Almost one-quarter of children in NZ received at least one dispensing within the first year of life (Figure 1). One-half of children received at least one dispensing by three years of age. By the age of five years, 55.2% of children had received at least one dispensing. By five years of age, children of Pacific ethnicity, those in the highest deprivation quintile, and in those non-urban health districts had lower odds of receiving chloramphenicol (adjusted OR 0.90, 0.79, and 0.81, respectively, all $p < 0.001$, Table 1). In contrast, children of Māori ethnicity had higher odds (adjusted OR 1.99, $p < 0.001$).

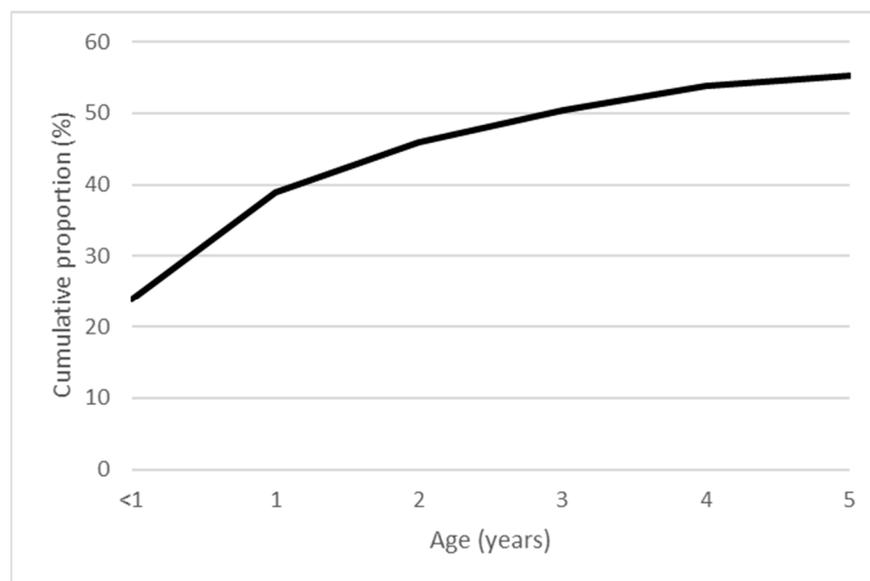


Figure 1. Cumulative proportion of children in NZ dispensed ophthalmic chloramphenicol.

The dispensing rate for ophthalmic chloramphenicol in NZ was 0.17 dispensings per person-year by five years of age (95% CI 1.72, 1.78). Following multivariate analysis, Māori and Pacific ethnicity were independently and significantly associated with fewer dispensings by five years of age, compared with non-Māori/non-Pacific ethnicity (Table 2). This was more pronounced among children of Pacific ethnicity (IRR (95% CI) 0.75 (0.72, 0.79)) compared with children of Māori ethnicity (0.88 (0.86, 0.90)). Residence in non-urban health districts was also independently and significantly associated with fewer dispensings by five years of age, compared with residence in urban health districts (0.87 (0.85, 0.89)). In contrast, there were no statistically significant differences in dispensing rate between the lower and higher socioeconomic deprivation quintiles.

Table 1. Cumulative proportion of children dispensed ophthalmic chloramphenicol by one, three, and five years of age, by ethnicity, urban/non-urban health district, and deprivation quintile (OR: odds ratio, CI: confidence interval, * denotes statistical significance).

		1 Year Of Age					3 Years of Age					5 Years of Age				
		%	Unadjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value	%	Unadjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value	%	Unadjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
Ethnicity	Māori	27.45	1.82 (1.74, 1.90)	<0.001 *	1.85 (1.76, 1.93)	<0.001 *	49.53	1.82 (1.74, 1.90)	<0.001 *	1.85 (1.76, 1.93)	<0.001 *	57.28	1.88 (1.81, 1.96)	<0.001 *	1.99 (1.92, 2.07)	<0.001 *
	Pacific	16.53	0.95 (0.89, 1.01)	0.15	0.94 (0.87, 1.00)	0.09	31.58	0.95 (0.89, 1.01)	0.15	0.94 (0.87, 1.00)	0.09	38.83	0.89 (0.85, 0.94)	<0.001 *	0.90 (0.86, 0.95)	<0.001 *
	Non-Māori/ non-Pacific	17.20	Reference	Reference	Reference	Reference	34.05	Reference	Reference	Reference	Reference	41.52	Reference	Reference	Reference	Reference
Deprivation quintile	1 (least deprived)	19.57	Reference	Reference	Reference	Reference	38.17	Reference	Reference	Reference	Reference	47.33	Reference	Reference	Reference	Reference
	2	17.89	0.89 (0.83, 0.95)	0.001 *	0.88 (0.82, 0.94)	<0.001 *	35.64	0.89 (0.83, 0.95)	0.001 *	0.88 (0.82, 0.94)	<0.001 *	43.16	0.84 (0.80, 0.89)	<0.001 *	0.83 (0.79, 0.88)	<0.001 *
	3	17.36	0.86 (0.80, 0.92)	<0.001 *	0.83 (0.78, 0.89)	<0.001 *	34.66	0.86 (0.80, 0.92)	<0.001 *	0.83 (0.78, 0.89)	<0.001 *	41.31	0.78 (0.74, 0.82)	<0.001 *	0.76 (0.72, 0.80)	<0.001 *
	4	20.49	1.06 (0.99, 1.12)	0.06	1.00 (0.93, 1.06)	0.99	38.83	1.06 (0.99, 1.12)	0.06	1.00 (0.93, 1.06)	0.99	46.43	0.96 (0.91, 1.01)	0.15	0.92 (0.87, 0.97)	0.003*
	5 (most deprived)	19.93	1.02 (0.96, 1.08)	0.45	0.91 (0.85, 0.97)	0.004 *	36.85	1.02 (0.96, 1.08)	0.45	0.91 (0.85, 0.97)	0.004 *	43.97	0.87 (0.83, 0.91)	<0.001 *	0.79 (0.75, 0.83)	<0.001 *
Health district	Urban	19.21	Reference	Reference	Reference	Reference	37.19	Reference	Reference	Reference	Reference	45.00	Reference	Reference	Reference	Reference
	Non-urban	18.89	0.97 (0.93, 1.02)	0.35	0.89 (0.85, 0.93)	<0.001 *	35.64	0.97 (0.93, 1.02)	0.35	0.89 (0.85, 0.93)	<0.001 *	42.15	0.89 (0.86, 0.92)	<0.001 *	0.81 (0.78, 0.84)	<0.001 *

Table 2. Number of ophthalmic chloramphenicol dispensings per person-year by five years of age, by ethnicity, urban/non-urban health district, and deprivation quintile (CI: confidence interval, * denotes statistical significance).

		Number of Dispensings Per Person-Year (95% CI)	Adjusted Incidence Rate Ratio (95% CI)	p Value
Ethnicity	Māori	0.216 (0.213, 0.220)	0.883 (0.860, 0.908)	<0.001 *
	Pacific	0.138 (0.134, 0.142)	0.759 (0.726, 0.792)	<0.001 *
	Non-Māori/ non-Pacific	0.169 (0.168, 0.171)	Reference	Reference
Deprivation quintile	1 (least deprived)	0.195 (0.191, 0.199)	Reference	Reference
	2	0.174 (0.170, 0.177)	0.989 (0.955, 1.204)	0.546
	3	0.166 (0.163, 0.169)	0.992 (0.959, 1.028)	0.684
	4	0.182 (0.179, 0.185)	0.984 (0.951, 1.018)	0.349
	5 (most deprived)	0.168 (0.165, 0.170)	1.011 (0.976, 1.047)	0.539
Health district	Urban	0.195 (0.191, 0.199)	Reference	Reference
	Non-urban	0.174 (0.171, 0.177)	0.874 (0.851, 0.897)	<0.001 *

The distribution of ophthalmic chloramphenicol dispensings was fairly stable throughout the year, except for a broad peak around August and September. This seasonal dispensing pattern remained fairly similar across ethnicities, deprivation quintiles, and urban/non-urban health districts. Following stratification by age, dispensings for children aged 0–4 years also exhibited this seasonal pattern; however, dispensings for children five years of age increased steadily throughout the year (Figure 2).

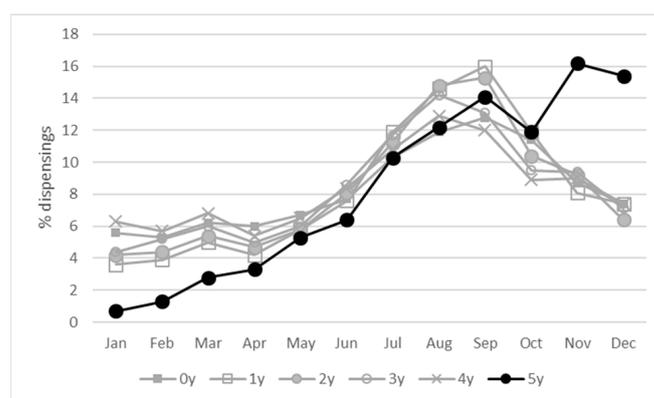


Figure 2. Seasonality of ophthalmic chloramphenicol dispensings, by age.

3. Discussion

This study generated new evidence on the paediatric utilisation of ocular chloramphenicol across NZ. The literature on such use at a population level is limited; however, Andersson et al. also reported the paediatric utilisation of ocular antibiotics to be relatively prevalent across Scandinavia (especially early in life) [14].

This study found that utilisation was prevalent among NZ children and began early in life. Though indications were not captured in the dataset used (which was a limitation of this analysis), it is possible that the high usage of chloramphenicol partially reflects its inappropriate use in non-infectious (such as allergic) and viral conjunctivitis, both highly prevalent conditions [5,6]. Although evidence of substantial clinical benefit is limited, topical antimicrobials are often prescribed in the management of acute bacterial conjunctivitis [2,3], which likely also contributes to the high usage of chloramphenicol. Chloramphenicol is likely to be the most commonly prescribed therapy for this condition in NZ, as it is by far the most commonly used ocular antibiotic across NZ [13]. In other countries, ciprofloxacin, norfloxacin, gentamycin and tobramycin are also prescribed for the management of acute bacterial conjunctivitis [3], although evidence supporting usage of topical antimicrobials in this condition is limited [2]. Utilisation was lower in non-urban health districts. It is possible that there is a lower density of healthcare providers in less densely populated areas [15], and poorer access may reduce healthcare seeking behaviour for potentially minor or self-limiting conditions [16]. We also hypothesise that children in less densely populated environments in NZ could potentially have less opportunity to transmit infective conditions such as acute bacterial conjunctivitis, and thus potentially have lower ocular infection rates, although this remains to be described. Additionally, prescribing behaviours and attitudes among healthcare providers may differ between urban and rural areas [17]. One limitation of this study was that some health districts classified as urban also cover large rural areas. Nonetheless, these findings help highlight possible disparities in eye care provision across NZ.

Children in higher deprivation deciles had lower odds of receiving chloramphenicol; this may again potentially reflect poorer healthcare access [18]. Utilisation was also lower among children of Pacific ethnicity, compared with non-Māori/non-Pacific children. In contrast, children of Māori ethnicity had higher odds of receiving chloramphenicol, although the quantity received was lower than non-Māori/non-Pacific children. It is unknown whether bacterial ocular infections are also more common among Māori children. However, other ocular infections (such as herpes simplex keratitis) have been reported to be more common among Māori [19]. Of note, the potentially higher utilisation of ophthalmic chloramphenicol among Māori was independent of deprivation and residence in less urbanised areas. These factors have been put forward as potentially contributing to lower healthcare use among Māori [20,21]. With regard to chloramphenicol utilisation, Māori ethnicity itself may potentially relate to other unknown factors, which subsequently contribute to potentially higher usage. Such insight would help address eye health gaps between Māori and non-Māori/non-Pacific across Aotearoa/NZ.

Overall, utilisation was fairly stable throughout the year, except for a broad peak around August and September, which coincides with the Southern Hemisphere winter [22]. Increased usage could partially be attributed to an increased incidence of respiratory infections such as influenza, during which conjunctivitis often manifests [23]. It is also possible that increased time spent indoors may increase potential opportunities for conjunctivitis transmission. It is unclear why chloramphenicol utilisation in children aged five years differed from that in younger children and increased steadily throughout the year. Further work is underway to describe wider factors in ocular antibiotic usage, including in older children.

One limitation of this study was that subsidy-ineligible dispensings (those dispensed by pharmacists without a prescription) were excluded, as these dispensings were unavailable in the utilised dataset. These dispensings could impact the utilisation patterns observed; however, these dispensings are expected to have a relatively small effect on the study findings, as pharmacist dispensing of ophthalmic chloramphenicol (without a prescription) is restricted to patients aged over two years; however, most dispensings of this medication are accounted for by children aged under two years.

In conclusion, the paediatric utilisation of ocular antibiotics across NZ is high, varies by patient and healthcare factors, and exhibits temporal patterns. Such research will help inform broader initiatives in health equity and antibiotic stewardship in ocular conditions.

4. Materials and Methods

This study analysed anonymised dispensing data from a nationwide dataset for publicly subsidised medications. Population denominators were obtained from the NZ census. Ethical approval for this research was granted by the Auckland Health Research Ethics Committee (reference AH21886, approved on 21 January 2021).

This study analysed every subsidy-eligible community dispensing of ophthalmic chloramphenicol in NZ, between 1 January 2013 and 31 December 2018, for individuals with a year of birth of 2013. As such, this collated all dispensings received by an individual between birth and five years of age.

This study included subsidy-eligible dispensings; ophthalmic chloramphenicol is eligible for subsidisation when prescribed for approved indications as per the NZ Pharmaceutical Schedule [24]. In NZ, ophthalmic chloramphenicol can also be dispensed by pharmacists without a prescription, for individuals aged over two years; these dispensings are not eligible for subsidisation and thus are not included in the analysed dataset. This study included chloramphenicol eye ointment 1% and eye drops 0.5%; dispensings for both formulations were pooled for analysis.

This analysis described drug utilisation by the number of dispensings, rather than Defined Daily Doses (DDDs). As a topical medication, a DDD for ophthalmic chloramphenicol is unavailable [25]. However, dispensings were considered to be an appropriate measure, as one dispensing typically represents one course of ophthalmic chloramphenicol.

The following measures of drug utilisation were quantified: cumulative proportion of first exposure by one, three, and five years of age, dispensing rate per person-year by five years of age, and seasonality of dispensings. These measures were calculated following stratification by prioritised ethnicity [26], socio-economic deprivation, and urban/non-urban health district. Māori and Pasifika are the indigenous populations of NZ and the South Pacific islands, respectively. Socio-economic deprivation was based on NZDep2013 Index of Deprivation deciles [20], which were combined into equally sized quintiles, with quintile 1 the least deprived and quintile 5 the most deprived.

Patients' domicile health district was classified urban or non-urban for this study. During the study period, NZ was geographically divided into 20 health districts. District offices provided publicly funded health services within their catchments. The following health districts were classified urban: Auckland, Waitemata, Counties Manukau, Capital and Coast, Canterbury, Waikato, Bay of Plenty, Southern and Hutt Valley. These served a Major Urban Area; specifically: Auckland, Wellington, Christchurch, Hamilton, Tauranga, Dunedin and Lower Hutt [27]. All urban health districts were aggregated for analysis. The remaining 11 health districts were classified non-urban and aggregated for analysis.

Data and statistical analyses were performed using IBM SPSS Statistics version 26 (Armonk, NY, USA). Multivariate logistic regression was used to determine the association of ethnicity, residence in urban/non-urban health district and deprivation with first exposure by one, three and five years of age. Unadjusted and adjusted (by all other factors) odds ratios (OR) with 95% confidence intervals (CI) were determined. Zero-inflated Poisson regression was used to determine the association of ethnicity, residence in urban/non-urban health district and deprivation with dispensing rate per person-year by five years of age, respectively. Adjusted (by all other factors) incidence rate ratios (IRR) with 95% CI were determined. $p \leq 0.05$ was considered statistically significant.

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Informed Consent Statement: Not applicable.

Data Availability Statement: Restrictions apply to the availability of these data from the authors as this is national administrative health data collected and provided by, and used by the authors with the permission of, Manatū Hauora Ministry of Health.

Conflicts of Interest: The authors declare no conflicts of interest.

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