THE EPIDEMIOLOGY OF INFECTIOUS DISEASE IN THE *GROWING UP IN NEW ZEALAND* COHORT STUDY

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ABSTRACT

Aim: New Zealand children suffer from high rates of infectious disease (ID) in general, and of skin and soft tissue infections (SSTI) in particular. Māori and Pacific children, and children in the most socioeconomically deprived households, are the most severely affected. This thesis sought to measure these ethnic and socioeconomic disparities, and determine the contribution of host, environmental and pathogen factors to the epidemiology of infectious disease in children enrolled in the *Growing Up in New Zealand* cohort study.

Methods: Linkage was established between data obtained from interviews with the primary caregivers of cohort children, national administrative health datasets, and the results of bacterial cultures from the nose, throat and skin of cohort children, including genotyping results from isolates of *Staphylococcus aureus* and *Streptococcus pyogenes*. Unadjusted and multivariable regression adjusted associations between infection outcomes and explanatory variables were determined.

Findings: Cohort children received a median of 8 antibiotic prescriptions dispensed by the age of five years, with Māori and Pacific children receiving a median of 9 and 11 courses respectively, and children living in the most deprived areas receiving a median of 9 courses. Hospitalisations for an infectious disease affected 25.6% of cohort children. Māori and Pacific ethnicity and reduced access to primary healthcare were associated with an increased risk of having had a hospitalisation for an ID. Māori and Pacific children were also disproportionately affected by community-onset SSTI. When considered independently, *S. aureus* and *S. pyogenes* colonisation were both associated with an increased risk of SSTI. However, when co-colonisation with both organisms was accounted for, colonisation with either organism alone was no longer associated with an increased risk of SSTI. Within the subset of children colonised with *S. aureus*, the genotype of *S. aureus* they were colonised with did not appear to affect the risk of SSTI, however, colonisation with a methicillin-resistant strain or with multiple strains increased the risk.

Conclusions: Māori or Pacific ethnicity and socioeconomic deprivation were associated with an increased risk across a broad range of ID-related health outcomes. These associations were only partly explained by the measured host, environmental, and bacterial factors. The remaining associations may be due to residual confounding and unmeasured factors.

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CHAPTER 1: INTRODUCTION

1.1 INFECTIOUS DISEASE AND SKIN AND SOFT TISSUE INFECTION IN NEW ZEALAND CHILDREN

The incidence of infectious disease (ID) amongst children in New Zealand (NZ) is higher than in comparable developed nations (1). For example, in the United States of America (USA) between 1998 and 2006, the incidence of hospitalisation for an ID was 6926/100,000 for children less than 1 year old and 1408/100,000 for children between 1 and 4 years old, while in NZ between 2004 and 2008 it was 9108 for children between 0 and 4 years old (1, 2). The incidence of ID follows a 'J-shaped' curve with regards to age, with the highest rates seen in children under five years of age and in the elderly. Epidemiological studies in NZ have consistently shown major ethnic and socioeconomic disparities in ID rates, with Māori and Pacific children and those living in the most economically deprived parts of the country being more severely affected (1, 3-7). Furthermore, rates of admission to hospital for an ID, and the ethnic and socioeconomic disparities in these rates increased between 1989 and 2008 (1). Previous work conducted in the *Growing Up in New Zealand* cohort showed that these disparities were evident even within the first year of life (8). Māori and Pacific peoples are disproportionately affected by socioeconomic deprivation, poor housing, exposure to racism, and other inequities which contribute to poor health outcomes, particularly for ID (5, 7). Internationally, similar ethnic disparities are seen when rates of ID for Aborigines and Torres Strait Islanders are compared with those for non-indigenous people in Australia (9, 10), and when rates of ID for Native Americans, Inuit and African Americans are compared with those for Whites in the USA (2, 11, 12).

These ethnic and socioeconomic disparities are particularly pronounced for skin and soft tissue infections (SSTI). The incidence of SSTI peaks in the first five years of life (13). SSTI is a common cause for hospital admission in New Zealand children – between 2000 and 2007 the incidence of admission for children with SSTI doubled, and was highest in children between 0 and 4 years old at 733/100,000 children/year (14). The rates of hospitalisation for SSTI in Māori and Pacific children are significantly higher at 2.67 and 4.56 times the rates seen in non-Māori, non-Pacific children in NZ respectively – these rates are amongst the highest reported in developed countries (6). Disparities by geographic region, largely related to the distribution of poverty, are also marked (4). Similar disparities in hospitalisation rates for

SSTI have been observed in Aboriginal children in Australia, and in indigenous children in the USA (9-11, 15).

The spectrum of SSTI extends from superficial infections such as impetigo, to abscesses and cellulitis which can be associated with sepsis and a need for hospitalisation, and further to life-threatening but thankfully rare conditions such as necrotising fasciitis. Even mild skin infections can lead to significant social stigma and isolation, and can lead to serious medical complications. For example, impetigo can lead to post-streptococcal glomerulonephritis (16-19), and in regions where impetigo is endemic but streptococcal pharyngitis is relatively rare, impetigo is also thought to act as a precipitant of rheumatic fever (20). While children with severe SSTIs may need hospital admission and can therefore be counted using discharge coding data, an overwhelming majority of children with SSTI are managed at home, with or without seeking medical attention in primary care, thus making it difficult to accurately estimate the true burden of disease (21). Previous research which examined the results of community laboratory swabs indicated that more than 2% of the population suffered *Staphylococcus aureus* SSTI each year (22). A study in the Tairawhiti region of NZ – an area with a high burden of SSTI – found that 10.7% of children sought primary care for an SSTI each year compared with 0.8% who were admitted to hospital (21). In research conducted in young children in tropical north Australia – also an area with a high burden of SSTI – 40% had at least one episode of pyoderma (impetigo or abscess) (20).

The epidemiology of ID is often described using the framework of the 'epidemiological triad', the three factors making up the triad being the host, the pathogen, and the environment. Host factors include genetic or epigenetic variants, comorbid conditions, particularly those that damage innate immune barriers such as the skin or gut mucosa, medications which suppress the immune system, and behaviours which increase or reduce the risk of infection (for example, injecting drug use). Pathogen factors include virulence factors such as expression of adhesion molecules and toxins, nutritional capabilities, methods of avoiding killing by the host immune system, and antibiotic resistance mechanisms. Lastly, environmental factors include seasonal or climatic variation, and features of the household, occupational, or recreational environments the host may have visited or been exposed to. These environmental factors include the availability of clean food and water, non-crowded living conditions, and facilities to maintain personal hygiene.

SSTIs are a good example of a group of conditions which can be understood and investigated using the epidemiological triad as a framework. For SSTI, relatively little is known about host genetic susceptibility, excluding a small number of rare primary immune deficiency disorders such as chronic granulomatous disease. A number of gene variants have been identified, for example in the glucocorticoid receptor gene, which predispose to persistent *S. aureus* nasal colonisation (23, 24), and persistent colonisation is associated with an increased risk of hospital-acquired infection (25, 26). While some authors have suggested that the marked ethnic disparities seen in SSTI rates could have a genetic basis, it is important that disparities are not attributed to genetic causes without fully accounting for shared environmental factors, particularly disparities in the social determinants of health (27, 28). Comorbid conditions affecting the skin, such as eczema or scabies, are important host factors at all ages, as are obesity, diabetes and vascular disease in adults (17, 29). With regards to pathogen factors, the majority of SSTI are caused by a small group of organisms – *S. aureus* and the β-haemolytic streptococci (predominantly *Streptococcus pyogenes*). In the case of *S. aureus*, production of toxins such as the Panton-Valentine leucocidin has been associated with SSTI (30, 31), as has the spread of community-acquired methicillin-resistant *S. aureus* (MRSA) clones, which often carry genes for this toxin and other virulence factors (32, 33). Environmental contributions to SSTI are less clear, other than exposure to socioeconomic deprivation. The ability to clean the skin is probably important – research undertaken in Australia, including a 2016 systematic review, showed that the introduction of chlorinated swimming pools to remote Aboriginal communities with high rates of SSTI led to a reduction in those rates (34, 35). Climate also appears to be a factor as rates of SSTI are much higher in the tropics than in the temperate zones, although economic development may also be an important influence on this observation (36).

1.2 THE *GROWING UP IN NEW ZEALAND* COHORT

The *Growing Up in New Zealand* (GUINZ) longitudinal birth cohort is well placed to examine disparities in health outcomes in NZ children. The GUINZ cohort is large, with 6822 mothers recruited in the antenatal period (37). The 6853 children born to these mothers are representative of the current national birth cohort with regards to ethnicity and socioeconomic status (38, 39). Participants were enrolled from the contiguous Auckland, Counties-Manukau and Waikato District Health Board areas; particular care was taken in the selection of the study

region to ensure adequate enrolment of Māori and Pacific children. Major data collection waves, with computer-assisted face-to-face interviews with each child's primary caregiver (and in 64.5% of cases, with the primary caregiver's partner as well), occurred during the antenatal period, at 9 months, and at 2 and 4½ years. Further data has been obtained from computer-assisted telephone interviews conducted between the major data collection waves. Detailed information is available from these interviews regarding parental and child ethnicity, child nutrition including breastfeeding duration, health status, period-prevalence of common childhood conditions including skin infections and eczema, and the household environment including socioeconomic factors, crowding, tobacco smoking, heating sources, and urban or rural location. Where primary caregivers have consented, the cohort children have had their GUINZ data linked to national administrative health datasets which include data on birth hospital perinatal records, the administration of scheduled childhood immunisations, the dispensing of prescribed medications from community pharmacies, and admissions to hospital. At the data collection wave conducted at 4½ years of child age, again with their primary caregiver's consent, the cohort children had swabs collected from the nose, throat and skin (40). These swabs were cultured to identify *Staphylococcus aureus* and *Streptococcus pyogenes*, and were stored for potential future investigations.

Given the features of the cohort described, the data and resources available for the GUINZ cohort provide an excellent opportunity to examine the epidemiological triad underlying SSTI. In terms of SSTI outcomes, hospital admissions for SSTI can be identified from linkage to the National Minimum Dataset (41), and children affected by SSTI in the community can be identified from interview data. Interview data are available regarding host factors including ethnicity, sex, and the presence of some common predisposing medical conditions such as eczema, while linked data are available documenting immunisation status (42) and perinatal risk exposures such as preterm delivery and low birthweight. At this stage host genetic information is not available due to the cost of conducting whole genome sequencing or microarray testing for such a large number of children. Some pathogen factors can also be addressed. Colonisation status with *S. aureus* and *S. pyogenes* is known, albeit only at a single, cross-sectional time point. Repeated sampling would have been preferable to determine the persistence of bacterial colonisation over time but was not feasible given the size of the cohort. However, it is possible to infer persistent nasal carriage of *S. aureus* if a heavy density of growth is observed on culture (43). Antibiotic resistance, including methicillin resistance, was determined for isolates of *S. aureus*. In addition, a majority of the isolates of *S. aureus* and *S. pyogenes* were stored and were available for genotyping by *spa*-

typing and *emm*-typing respectively (44-46). Lastly, GUINZ has data on environmental exposures, particularly regarding the household environment, and the longitudinal nature of the cohort allows tracking of changes in exposures over time. This data comes from the interviews and from linkage with Statistics New Zealand data regarding socio-economic deprivation (NZDep2006 and 2013) (47, 48) and urban or rural location, derived from the stated place of residence for each child (49).

As a requirement of ethics approval, GUINZ has a policy of not publishing results with cell sizes (or counts of participants) where the cell size is less than 10 participants. This is to avoid potential identification of participants. Therefore, all tables in this thesis will display cells with a cell size of less than 10 participants as "<10".

1.3 INTENT AND STRUCTURE OF THIS THESIS

The objective of this thesis is to use the strengths of the GUINZ cohort to examine the burden of ID in general, and SSTI in particular, in NZ children up to the age of five years. The thesis focusses on identifying ethnic and socioeconomic disparities in disease incidence and examining the factors which lead to these disparities. Multivariable methods have been used to identify disparities while accounting for differences in environmental exposures. This thesis is structured in accordance with the University of Auckland's guidelines for theses with publications. With the exception of the Literature Review and Expanded Methodology chapters, each chapter is presented as an article which has been published, or is suitable for submission for publication, in a peer-reviewed medical journal. As such, there is some repetition of introductory and methodological material between chapters. There is also variation in which explanatory variables have been selected for inclusion, dependent on the outcome being examined and informed by prior research.

Chapter 2 is a review of the published literature from NZ and comparable countries describing ethnic disparities in ID outcomes. Comparable countries are taken to be those with a history of European colonisation and modern demography characterised by the presence of socioeconomically disadvantaged indigenous and ethnic minority populations, for example Australia, Canada, and the USA. Outcomes of interest include rates of hospitalisation for an

ID, of SSTI morbidity, of community antibiotic use, and of infection with specific pathogens such as *S. aureus* (particularly MRSA). The chapter finishes by describing literature looking at the causes of the observed ethnic disparities in ID outcomes.

Chapter 3 describes supplementary data management and laboratory research methods in greater detail than would be possible in a manuscript suitable for publication. It provides details on: the structure and linkage of core GUINZ datasets; derivation of new variables; exploratory data analysis; the structure and linkage of administrative health datasets (the National Minimum Dataset and Pharmaceutical Collection) including the process of cleaning these datasets; the structure and linkage of biological sample datasets; the laboratory processes related to bacterial genotyping; and, the data management of genotypic data.

Chapter 4 describes and compares methods of ascribing ethnicity and socioeconomic deprivation, drawing on data obtained from the interviews conducted when each child was 4½ years old. GUINZ has collected ethnicity data with sufficient detail to allow each child's ethnicity to be ascribed using self-prioritisation, total response and single-combined methodologies. Likewise, socioeconomic data is available in the form of household income, and census-derived and survey-derived indices of deprivation (the NZDep2013 and NZiDep respectively) (47, 50, 51).

Chapter 5 uses data from the linked Pharmaceutical Collection to estimate the degree of exposure to antibiotics experienced by cohort children up to the age of 5 years (52). Most of these antibiotic prescriptions will have been prescribed in response to a primary care attendance with an ID, so antibiotic use gives a rough estimate of the burden of community ID. The majority of ID and SSTI are managed either at home or in primary care (21), but no formal records are available regarding ID managed at home, and accurate information on ID managed in primary care is hard to obtain. While a variety of factors including illness severity lead families with young children to attend primary care rather than managing symptoms at home, the majority of infections managed in primary care remain mild and self-limiting, often of viral origin, and do not require antibiotics (53). Therefore, antibiotic use can also relate to the quality of primary care received.

Chapter 6 uses data from the linked National Minimum Dataset to identify hospitalisations for any type of ID, and estimates the effect of ethnic disparities and lack of access to primary care on the period-prevalence of hospitalisation for an ID, while accounting for a broad range of perinatal and environmental exposures. Hospitalisation for an ID generally occurs where onset has been sudden, or where intervention in the community has not been available, has not been sought, or has not been effective. This chapter puts SSTI in the wider context of the epidemiology of hospitalisation for an ID in childhood, which is dominated by a high rate of respiratory illness in the first two years of life.

Chapters 7, 8, 9, and 10 all describe rates of SSTI, including hospitalisations for SSTI identified using data from the National Minimum Dataset and community-managed SSTI using data from parental interviews. To address the pathogen arm of the epidemiological triad, each chapter links this outcome data with results from the culture of swabs collected from the nose, throat and skin of participating cohort children during the interview conducted at 4½ years of age.

Chapter 7 looks for associations between *S. aureus* colonisation and explanatory covariates, and between SSTI and *S. aureus* colonisation. SSTI outcomes are examined both in the year prior to the interview conducted at 4½ years of age, and over the entire period of the first 4½ years of life. *S. aureus* colonisation is defined as any colonisation, heavy nasal colonisation (a proxy for persistent nasal colonisation), and skin colonisation, with associations sought between each form of colonisation and each outcome.

Chapter 8 looks for associations between MRSA colonisation and explanatory covariates, and between SSTI and MRSA colonisation, within the subset of children who were colonised with *S. aureus*.

Chapter 9 investigates the potential role of different *S. aureus* strains in SSTI by incorporating genotyping of S. *aureus* colonising isolates using *spa*-typing (a genotyping method based on sequencing of a hypervariable region of the staphylococcal protein A gene). As not all isolates had been stored, only a subset of *S. aureus*-colonised children could be included in this study.

Chapter 10 looks for associations between *S. pyogenes* colonisation and explanatory covariates, and between SSTI and *S. pyogenes* colonisation. *S. pyogenes* isolates are also described in terms of their *emm*-type (sequencing of streptococcal M protein gene) but again, only for a subset of cohort children.

The thesis then concludes in Chapter 11 by reviewing the information gained in the preceding chapters and making suggestions for possible interventions and for further research directions both within the GUINZ cohort, and in general.

CHAPTER 2: LITERATURE REVIEW

2.1 INTRODUCTION

The main objective of this thesis is to examine the burden of infectious disease (ID) morbidity in children in the *Growing Up in New Zealand* (GUINZ) cohort, with a focus on skin and soft tissue infections (SSTI), and on the ethnic and socioeconomic disparities in the incidence of ID and SSTI. This chapter consists of a review of the published evidence of disparities in ID-related health outcomes, both in New Zealand (NZ) and in comparable countries. Outcomes of interest include hospitalisation for ID and SSTI, mortality from ID, and the level of community antibiotic use. Community antibiotic use provides an approximation of community ID burden, albeit one with caveats regarding healthcare access and prescriber behaviour. After considering disparities in ID and SSTI, this chapter will conclude by reviewing the evidence for the determinants of these disparities.

For the purposes of this review, comparable countries are taken to be those with historical and demographic similarities to NZ. The modern demography of NZ has been deeply impacted by historical patterns of migration to NZ of various ethnic groups. NZ has an indigenous Māori population and a history of European (predominantly British) colonisation, with NZ Europeans now making up the majority of the population. European migration to NZ continued throughout the 19th and 20th centuries, while the latter half of the 20th century saw substantial Asian and Pacific migrations to NZ (54). Currently, ethnic disparities in health are closely entwined with socioeconomic disparities. The NZ European population experiences relative socioeconomic and health advantage, while the Māori and Pacific populations experience significant socioeconomic and health disadvantage. Therefore, the features which identify comparable countries are taken to be: an advanced, first-world economy; a history of European colonisation; and, modern demography characterised by the presence of socioeconomically disadvantaged non-European ethnic minority and indigenous populations. Examples of such comparable countries include Australia, the United States of America (USA), and Canada.

2.2 DISPARITIES IN INFECTION-RELATED HEALTH OUTCOMES IN THE MĀORI AND PACIFIC POPULATIONS OF NEW ZEALAND

The Māori and Pacific populations in NZ experience adverse health outcomes due to both infectious and non-communicable diseases. Life expectancy, perhaps the most basic and important health outcome, is significantly lower for Māori and Pacific people compared with NZ Europeans. In 2012-2014, life expectancy at birth for Māori males and females was 72.98 and 77.15 years respectively, while for Pacific males and females it was 74.45 and 78.72 years, compared with 80.31 and 83.92 years for non-Māori males and females (55). Much of the deficit in life expectancy is related to higher rates of non-communicable disease – Māori and Pacific adults experience higher rates of obesity, type 2 diabetes, and ischaemic heart disease than do European adults (56).

While there are ethnic disparities in ID mortality rates in NZ, infections in childhood are only rarely life-threatening so the major ethnic disparities observed are in the rates of ID morbidity. Consequences of increased ID morbidity can include hospitalisation, disruption in parental employment and child schooling, and the potential for lifelong complications such as bronchiectasis and rheumatic heart disease.

In 2012, Baker *et al*. reported that ID accounted for 26.6% of hospitalisations in NZ between 2004 and 2008, and that there were significant disparities based on ethnicity and socioeconomic status (1). In this study the age-adjusted rate ratio for ID hospitalisations was 2.15 (95% CI 2.14-2.16) for Māori and 2.35 (95% CI 2.34-2.37) for Pacific people compared to people of European or other ethnicities. These inequalities increased over the period studied. For children under the age of 5 years, the rate ratio for ID hospitalisations for Māori children, compared with European or other children, increased from 1.63 (95% CI 1.62-1.65) in 1989-1993 to 2.05 (95% CI 2.04-2.07) in 2004-2008, an increase of 27.6%. For Pacific children, the rate ratio increased from 1.45 (95% CI 1.43-1.46) to 2.11 (95% CI 2.09-2.13) over the same period, an increase of 48.3%.

The disparities documented by Baker *et al*. are corroborated by those of the NZ Child and Youth Epidemiology Service (NZCYES), which produces regular reports documenting the

health status of children and young people in NZ. In their 2014 and 2015 reports NZCYES showed that, when compared with non-Māori, non-Pacific children, Māori and Pacific children aged 0-14 years had 1.61 and 3.82 times more hospitalisations for pneumonia, respectively (6, 7).

The disparities for the long-term sequelae of recurrent infection were even greater. As reported by the NZCYES in their 2014 and 2015 reports, compared with non-Māori, non-Pacific children, Māori and Pacific children had rates of acute rheumatic fever (ARF) that were 34.70 and 77.73 times higher, and rates of hospitalisation for bronchiectasis that were 7.48 and 9.69 times higher, respectively (6, 7). A 2008 study by Jaine *et al.* reported somewhat lower incidence rate ratios (Māori RR=10.0 and Pacific RR=20.7) that the NZCYES reports, but showed that for Māori the incidence of ARF increased between 1995 and 2005, while for non-Māori, non-Pacific children the incidence decreased (57). The difference in the ARF incidence rate ratio estimates reported by Jaine *et al*. and by NZCYES could be explained by improved diagnosis and reporting, or by a widening of the disparity in rates during the time interval between the two studies. With regards to bronchiectasis, a condition which is often due to recurrent childhood respiratory infection, it is noteworthy that Māori and Pacific children have been shown to have higher readmission rates after hospitalisation for respiratory illness (58). Most of the excess hospitalisations experienced by Māori and Pacific people in NZ are regarded as potentially avoidable, either through prevention or early treatment in primary care (59, 60).

The disparity seen in the incidence of ARF constitutes strong evidence that Māori and Pacific children suffer from more frequent infection with *Streptococcus pyogenes* (61). Ethnic disparities in rates of infection with other specific pathogens have also been documented. In this regard, diseases caused by *Staphylococcus aureus* have been the most studied in NZ. Māori and Pacific children and young people are disproportionately affected by *S. aureus* bacteraemia (62, 63), and are more likely to have serious *S. aureus* disease requiring treatment in a paediatric intensive care unit (64). A study conducted using community bacterial swab samples showed that Māori and Pacific people (in this case adults) with *S. aureus* infection were also more likely to be infected with a methicillin-resistant (MRSA) strain (22).

With regards to community antibiotic use, NZ is known to be a relatively heavy user when compared with European countries (65). However, there is relatively little data available comparing antibiotic use between ethnic groups. At an aggregate level, community antibiotic use is highest in District Health Boards with a high proportion of Māori and Pacific residents (65). Williamson *et al*. showed that antibiotic use was slightly higher in Pacific people and lower in Māori when compared to Europeans (66). However, a 2018 study by Whyler *et al.* found that antibiotic use was higher in both Māori and Pacific people when compared to Europeans, Asians and others (67). A series of studies about community antibiotic use by Norris *et al*. have also revealed somewhat conflicting results. In a 2005 study conducted in a single NZ town, antibiotic use was found to be greater in more socioeconomically deprived areas but ethnicity data was not available (68). However, in a 2011 study conducted across a wider region, rural Māori were less likely to receive antibiotics compared with rural Europeans and with urban Māori (who received antibiotics at a similar rate to urban Europeans) (69). In this latter study, no relationship was found between socioeconomic deprivation and antibiotic use – this may have been due to confounding caused by the high levels of deprivation in the same rural Māori communities where poor access to healthcare was thought to be leading to unexpectedly lower levels of antibiotic use.

2.3 DISPARITIES IN INFECTION-RELATED HEALTH OUTCOMES IN THE INDIGENOUS AND ETHNIC MINORITY POPULATIONS OF AUSTRALIA, CANADA, AND THE UNITED STATES OF AMERICA

The ethnic disparities identified in NZ are broadly consistent with those found in comparable countries, for example, Australia, Canada, and the USA. While all are socioeconomically developed with advanced healthcare systems and predominantly European populations, there are a number of differences relative to NZ. Important differences are that: the proportion of the population made up by indigenous peoples is lower (between 1% and 4%) (70) than the proportion of Māori in NZ (about 15%) (71); and the size, history and geographic region of origin of other socioeconomically disadvantaged ethnic minorities are also quite different. The terminology used to identify these populations and the frequency with which research papers report findings in relation to ethnicity varies significantly, making direct comparisons difficult.

In the case of Australia, the indigenous Aboriginal and Torres Strait Islander populations experience markedly increased rates of ID morbidity that are consistent with rates seen in developing countries. These disparities extend across the lifespan and across a wide range of infectious conditions (72). The frequency of ID managed in the community is hard to assess accurately in a way that allows comparison between ethnic groups. Studies performed within remote rural Aboriginal communities show an extremely high prevalence of common infections such as pyoderma (skin infection), scabies, otitis media, and other respiratory tract infections (17, 20, 73), with consequent high rates of antibiotic use (74). However, several recent studies that examined antibiotic use in Australia did not consider ethnicity or indigenous status in their analyses; possibly because this data was not available or because of differences in how antibiotics are dispensed in remote Aboriginal communities (75, 76).

In terms of hospitalisation, Carville *et al*. demonstrated that, in Western Australia, infections were the main cause for hospitalisation for both Aboriginal and non-Aboriginal children under the age of 2 years, but that Aboriginal children were hospitalised because of ID more than four times as often as non-Aboriginal children (9). A 2010 review article by O'Grady and Chang concluded that indigenous children were more than three times more likely to be hospitalised for lower respiratory infection and were ten times more likely to die from a respiratory illness (77). Furthermore, indigenous adults with bronchiectasis were younger and more severely affected than non-indigenous adults with bronchiectasis, likely on the basis of recurrent childhood infections (78, 79).

In a study that included data from most large Australian hospitals, Tong *et al*. reported that the incidence of *S. aureus* bacteraemia (SAB) in the indigenous population was almost six times that of the non-indigenous population (62.5 / 1000,000 in indigenous Australians compared with 10.6 / 100,000 in non-indigenous, IRR 5.9) (80). A similar study looking at SAB in children in both Australia and NZ showed that the indigenous children in Australia had an incidence of SAB that was three times greater than non-indigenous children, while Māori and Pacific children in NZ (grouped together in this paper) had an incidence of SAB that was more than five times greater than non-Māori, non-Pacific NZ children (81). Furthermore, while the odds of mortality due to SAB were no greater for indigenous children in Australia, they were

ten times greater for Māori and Pacific children compared with non-Māori, non-Pacific children in NZ (81).

A comparable situation to that which occurs in Australia is also present in Canada, where the indigenous population is comprised of First Nations and Inuit groups. While the climate of Canada is clearly very different to that of Australia, the experience of many indigenous peoples is similar, with significant numbers of First Nations and Inuit living in remote communities, often in inhospitable areas, and suffering from high rates of diseases associated with poverty, such as bacterial and parasitic infections (82). He *et al*. found that First Nations and Inuit infants in Canada had an incidence of hospitalisation for ID that was approximately twice as high as that for non-indigenous infants (83). In this study ICD chapters were used to designate types of conditions, so many common infections were coded by organ system rather than as ID – e.g. pneumonia was coded as respiratory. As such, First Nations and Inuit infants had rates of hospitalisation for respiratory disorders that were 2.64 and 2.74 times higher than rates for non-indigenous Canadians. Similarly, in their 2017 report, Carriere *et al*. showed that First Nations people had almost three times greater odds of hospitalisation for respiratory infections compared with non-indigenous people (84). When the authors adjusted for household crowding, quality, and income using multivariable methods, the odds ratio relating First Nations identity to hospitalisation for respiratory infection was reduced (e.g. from 3.85 to 2.83 for those living on reserves) but remained elevated and statistically significant.

A relationship between disease incidence and indigenous ethnicity and poverty is likewise seen for ARF. While ARF is very rare in Canada, in recent years outbreaks have occurred in isolated and impoverished indigenous communities with substandard housing (85). With regards to specific pathogens, invasive infections with *S. pyogenes*, *S. pneumoniae*, and *Haemophilus influenzae* have been shown to occur at markedly higher rates in First Nations populations than in the general Canadian population (86, 87). As in Australia, many studies of community antibiotic use in Canada have not commented on ethnicity or indigenous status when reporting their findings (88-90). Where socioeconomic status has been considered, higher rates of community antibiotic use and a smaller decrease in use over time are evident for children from poorer socioeconomic backgrounds (91).

The situation in the USA is somewhat different in that discussions about ethnic disparities in healthcare often focus on poorer outcomes amongst Black / African American and Hispanic / Latino communities rather than amongst Native Americans and Alaska Natives (NA/AN). While the concept of race is seldom used outside the USA, many US authors and US government publications report on both race (Asian American, Black / African American, NA/AN, Native Hawaiian / Pacific Islander, or White American) and ethnicity (Hispanic / Latino, or not Hispanic / Latino) using the system followed by the federal Census Bureau (92). Depending on the size and ethnic mix of the population studied, many studies including those published in major international journals, simply fail to mention the NA/AN populations at all (93).

Research reports about ID epidemiology in the US, produced by authors based at the Centers for Disease Control, have identified a significantly increased incidence of hospitalisation for ID amongst the non-Hispanic Black and Hispanic groups compared with non-Hispanic White, while a combined Asian/Pacific Islander group had a lower incidence of ID hospitalisation, with the same pattern evident in infants and across the age range (2, 94). These papers did not focus on NA/AN.

In 2001, Holman *et al*. reported that NA/AN had a 21% higher incidence of hospitalisation for ID than the general population (95). In a 2003 paper the same group showed that ID accounted for 53% of hospitalisations for NA/AN infants compared with 43% for infants in the general population, while the incidence of ID hospitalisations per 100,000 infants was 47% greater for NA/AN infants than for infants in the general population (96). In a 2011 update of this work, Holman *et al*. showed that while NA/AN across the age spectrum had only a slightly higher incidence of ID hospitalisation than the general population (albeit with significant regional variability), NA/AN children under the age of 5 years had a 40% greater incidence of ID hospitalisation than children of this age in the general population. In a 2014 paper, Person *et al*. showed that NA/AN (RR 1.6) and Black infants (RR 2.6) had a significantly increased risk of ID-related mortality compared with White infants (97). Similarly, Wong *et al*. showed that NA/AN children had an increased risk of all-cause mortality compared with White children, with the most common causes of death being congenital malformation and sudden infant death syndrome; however, the most significant ethnic disparity was in death from influenza or pneumonia with a rate ratio of 4.97 (12).

With regards to antibiotic use, several recent papers have suggested that non-Hispanic Black children are less likely to receive antibiotics for viral respiratory infections in paediatric emergency departments (98), and less likely to receive antibiotics for otitis media diagnosed in ambulatory care settings (99). The implication in both cases being that their treatment was more concordant with guidelines than the treatment received by non-Hispanic White children. Similarly, a 2018 paper by Schmidt *et al*. showed that Black and Asian patients were less likely to receive antibiotics when presenting to ambulatory care practices with common respiratory conditions for which antibiotics were not indicated – this was true for both children and adults (100).

2.4 DISPARITIES IN SKIN AND SOFT TISSUE INFECTION MORBIDITY IN NEW ZEALAND AND IN COMPARABLE COUNTRIES

Skin and soft tissue infections (SSTI) are a significant contributor to ID morbidity, especially in children and young people. Common SSTI include abscesses, cellulitis, and impetigo. SSTI occur at high rates in children under 10 years of age and in the elderly but are relatively less frequent in working age adults (13). SSTI occur in all countries but particularly high rates are seen in developing countries and countries with a tropical climate (36). In developed nations such as NZ, SSTI are strongly associated with poverty, with markedly different rates occurring in different regions or population groups. For example, in a 2012 study, O'Sullivan *et al.* showed that the Tairawhiti region (a part of NZ with a large Māori population and a high rate of poverty), had an incidence rate for serious SSTI that was almost twice that of the national average (14).

In NZ, the rates of SSTI experienced by Māori and Pacific children are significantly higher than those experienced by non-Māori, non-Pacific children (101). Rates of attendance at primary care for SSTI can be hard to ascertain without manually going through practice records, making it difficult to estimate the burden of SSTI managed in the community. When O'Sullivan and Baker reviewed cases of SSTI seen by a sample of general practitioners (again in the Tairawhiti region), they found rates of diagnosis in Māori children that were almost four times greater than in non-Māori children in the 0-4 year age group, almost three times greater

in the 5-9 year age group, and over 4 times greater in the 10-14 year age group (21). Rates of diagnosis in primary care were 14 times greater than rates of hospitalisation for SSTI (21). As mentioned previously, when affected by an SSTI, Māori and Pacific people in NZ are more frequently infected with MRSA (22).

Rates of hospitalisation for SSTI are easier to determine provided strict definitions are used (102). These rates also show marked ethnic disparities in NZ (103, 104). In the 2015 and 2017 NZCYES reports on Māori and Pacific child health, Māori and Pacific children aged 0-14 years had 2.67 and 4.56 times more hospitalisations for serious SSTI when compared with non-Māori, non-Pacific children, respectively (6, 7). In contrast, some recent evidence suggests that the number of hospitalisations for SSTI in NZ may now be decreasing, driven by a decrease in ethnic and socioeconomic disparities in SSTI rates (105). The authors of this more recent study suggest that this closing of the gap could be in part related to school- and primary care-based interventions targeting these high-risk groups. Such interventions have been rolled out in high-prevalence areas with the intention of combatting rheumatic fever as well as SSTI (106, 107).

In Australia, SSTI are endemic amongst children and young people in many Aboriginal communities and occur so frequently that having recurrent SSTI has become normalised (73, 108). Scabies – a parasitic infestation of the skin – has also been identified at extremely high prevalence rates, and predisposes affected children to secondary bacterial infection (29, 73). The pressure of infection is such that many children in these communities begin suffering from scabies and SSTI within their first year of life (109). Aboriginal children also suffer high SSTI hospitalisation rates – Abdalla *et al*. estimated that Aboriginal children were hospitalised for SSTI at a rate 15 times higher than that of non-Aboriginal children (110).

The observation that SSTI and ARF are co-endemic in many remote Aboriginal communities, while streptococcal pharyngitis is relatively rare, has led some authors to suggest that recurrent streptococcal SSTI may be the major driver of rheumatic fever in these communities, with pharyngitis playing a lesser role (20). In recent years, community-acquired MRSA has been increasingly frequently implicated in SSTI in Aboriginal children, at much higher rates than those seen in non-Aboriginal children (81, 111, 112).

Canadian First Nations children also suffer an increased burden of SSTI. In the study by He *et al.*, First Nations and Inuit infants had incidence rates of hospitalisation for skin disorders that were 6.13 and 4.84 times higher than the rates for infants in the general population, respectively (83). First Nations and Inuit people have also been found to suffer from community-acquired MRSA infections at a significantly higher rate than non-indigenous Canadians (113, 114).

In the USA, the incidence rate for hospitalisation for SSTI has risen significantly in recent years. This rise is thought to be due in part to the spread of the USA300 clone of caMRSA, which has become the predominant cause of SSTI in the USA (115, 116). African American children suffer from particularly high rates of SSTI and are also more likely to be hospitalised for an SSTI. In 2013, Gutierrez *et al*. found that Black children were approximately 1.5 times as likely as White children to be affected by *S. aureus* infection (117). When hospitalised, the length of stay and associated costs have been found to be higher for Black, Hispanic and other race children compared to White children (118). NA/AN children are also more often affected by SSTI – Holman *et al*. found that the incidence of hospitalisation for SSTI amongst NA/AN children was approximately 1.75 times that of the general population (11). A study of caMRSA infections in children in Hawaii found that 51% of cases occurred in Native Hawaiians, who made up only 24% of the population. In a population-based study of SSTI in people of all ages, Ray *et al*. found that African Americans had 1.8 times greater odds of being infected with MRSA (119).

2.5 EXAMINATION OF POSSIBLE CAUSES FOR ETHNIC DISPARITIES IN INFECTIOUS DISEASE MORBIDITY IN NEW ZEALAND AND COMPARABLE COUNTRIES

The previous sections have demonstrated that ethnic disparities in ID and SSTI morbidity affect indigenous and ethnic minority groups in NZ and comparable countries. These affected groups are genetically and geographically distinct from one another but have a common exposure to many adverse environmental and socioeconomic determinants of health. Despite

this, a genetic predisposition to infection is occasionally considered, most often for specific infection phenotypes such as SSTI (120). This hypothesis gains some plausibility from the observation that indigenous populations suffered from exceptionally high rates of morbidity and mortality from pathogens such as measles, smallpox, influenza, and tuberculosis, which were introduced by early European explorers and colonists (121). It was hypothesised that these diseases had been sufficiently prevalent in the Old World that the Europeans who spread them had some inherited resistance (121). However, it should be noted that the arrival of Europeans in these societies was often accompanied by major social disruption and material dispossession, which may explain these observations to some extent (28).

A number of gene variants have been identified which provide a degree of resistance to specific pathogens of evolutionary importance - for example, gene variants coding for various haemoglobinopathies have been maintained in populations whose ancestors were heavily exposed to malaria due to "heterozygote advantage" – carriers had reduced morbidity and mortality from malaria (122). However, a genetic cause is less plausible as an explanation for the increased rates of ID seen across the breadth of common infections in highly genetically distinct populations (28).

With specific regards to SSTI, there is no reason to suspect that populations at increased risk of SSTI have not been continuously exposed to *S. aureus* in the same way as other populations. In fact, there are some rare variants of *S. aureus* which continue to affect Australian Aborigines and appear to have diverged from ancestral *S. aureus* populations at a timeframe consistent with that of the peopling of Australia (123). This suggests that lack of exposure, and thus lack of genetic or acquired resistance, is unlikely to explain the excess SSTI rates seen in these populations. The genetic differences between races or ethnic groups are small in comparison with the genetic variation seen within ethnic groups, while differences in the environmental determinants of health are often more consistent (28).

Rather than a genetic explanation, it is likely that the intergenerational effects of colonisation and persistent socioeconomic disadvantage mediate many of the disparities experienced by ethnic minority and indigenous populations in post-colonial societies (124). Historical analyses suggest a temporal relationship between increased ethnic socioeconomic inequality

and increased ethnic health inequality (125). Data from NZ show a clear link between socioeconomic status and ID morbidity (1). However, disparities in relative socioeconomic position do not entirely explain the disparities observed – even when socioeconomic status is accounted for using multivariable regression, some residual effect related to ethnicity tends to remain, particularly for the most disadvantaged ethnic groups (126).

A lack of financial resources leads to exposure to a range of other social and environmental risk factors for infection. Factors related to housing and household crowding are particularly relevant. Baker and colleagues have demonstrated links between household crowding and ID, particularly meningococcal disease, in NZ (127, 128), while Bailie *et al*. have shown an association between household crowding and SSTI in remote Aboriginal communities in Australia (129).

Housing quality, the availability of heating and the mode of heating used are also important factors, particularly for respiratory infections. Visible mould in the child's bedroom has been associated with an increased risk of pneumonia in NZ children (130), while the use of gas heating in the child's bedroom, or as the sole mode of household heating, has been shown to be associated with an increased risk of hospitalisation for acute respiratory illness (131).

Researchers working in Canadian indigenous communities have identified an increased incidence of SSTI in households that lack access to running water for personal hygiene (132). The importance of access to water to clean the skin is underlined by the reduction in SSTI incidence observed in Australian Aboriginal communities after the construction of public swimming pools (34, 35).

Access to healthcare is also affected by financial resources. While healthcare for children in NZ is currently free of charge, there are numerous indirect costs which can affect access. These include the availability of time off work for the parent, transport costs, and the cost of unfunded medications. As mentioned above, Norris *et al*. showed that rural Māori children in

Tairawhiti received fewer antibiotic prescriptions that did urban and European children, likely due to difficulties accessing care (69).

Similar difficulties with access to care occur for ethnic minority and indigenous populations in comparable countries. A study by Ou *et al*. showed that Australian Aboriginal children were more likely to attend hospital outpatient clinics and less likely to attend general practices (10). In the USA, Black, Hispanic and NA/AN people are more likely to be uninsured which can limit their access to affordable healthcare (133).

Even where healthcare is accessed, the care received may not be equal. Reasons for this could include exposure to racism within the healthcare setting, and lower health literacy. Previous research in NZ showed that Māori were more likely to report being aware of their ethnicity and being exposed to ethnic discrimination (134). Māori were also more likely than NZ Europeans to report exposure to racism in a healthcare setting (135). Furthermore, correcting for exposure to racism or ethnic discrimination was shown to reduce ethnic differences in rates of poor self-rated health status (135). Interestingly, both self-identified and socially-assigned ethnicity (the latter being how other members of society view the individual's ethnicity) were related to self-rated health status (136).

When people describe experiences of racism they are often assumed to mean direct interpersonal racist speech or action, but healthcare organisations can also be institutionally or structurally racist, without anyone in the organisation necessarily intending for this to be the case (137). In recent years calls have been made to identify and challenge institutional racism in NZ, and in Australia (138), Canada (139), and the USA (137). Suggested methods for addressing institutional racism include improving cultural competence and inter-cultural communication skills amongst healthcare providers (138), as well as addressing structural or organisational factors in the way healthcare is delivered (137).

The concept of health literacy describes an individual's ability to comprehend information provided about their own or their child's health or medical condition. This can include an

understanding of when and where to present for healthcare, how to take medications, and the importance of preventative measures, adherence to medication, and follow up care. Poor health literacy can lead to delayed presentation with serious illness, poor adherence to treatment, and loss to follow up. Standardised measurements exist for determining health literacy but these are often long questionnaires. Recently, brief assessments of up to three questions have been developed to estimate a person's health literacy (140, 141). In NZ, approximately 56% of the population is believed to have low health literacy (142).

Because poor health literacy is so widespread and NZ Europeans are the largest population group, the most common ethnicity amongst those with poor health literacy is also NZ European. However, the Kōrero Mārama report on health literacy amongst Māori in NZ showed that Māori were significantly more likely to have poor health literacy compared to non-Māori across all income bands (143). Approximately 80% of Māori men and 75% of Māori women had poor health literacy, with younger and older adults more likely to have poor health literacy than those aged 25-50 years (143).

A similar government report from Australia showed that an equivalent proportion of the Australian population, approximately 60%, had poor health literacy, but did not report data for Aboriginal and Torres Strait Islander Australians (144). A directly comparable study in Canada obtained very similar results – about 60% of their population also had poor health literacy – but did not report whether the health literacy of indigenous Canadians was comparable with that of other Canadian population groups (145). Data from the USA showed that Black, Hispanic and NA/AN Americans had lower health literacy than White or Asian/Pacific Islander Americans (146).

2.6 CONCLUSIONS

This literature review presents numerous examples of an increased rate of ID morbidity and mortality amongst indigenous and ethnic minority populations in NZ and in comparable post-colonial nations with European majority populations – specifically Australia, Canada and the

USA. The disparities are particularly pronounced for conditions with a strong association with poverty, and with a crowded or deprived household environment, such as respiratory infections and SSTI. Such infections in early childhood can have lifelong consequences, such as rheumatic heart disease and bronchiectasis.

Numerous risk factors have been identified that partially explain these ethnic disparities, including socioeconomic status, and housing quality and crowding. However, accounting for social and environmental factors does not entirely explain the disparities observed.

Ethnic minority and indigenous populations are also known to more frequently experience institutional and interpersonal racism in healthcare settings, and may have lower health literacy. Interventions to reduce ID disparities should be directed at the basal socioeconomic and housing factors which predispose to infection and should address health needs in a culture-specific and culturally acceptable way.

CHAPTER 3: EXPANDED METHODOLOGY

The research projects that comprise the core of this thesis shared common underlying methodology. Each project sought to identify associations between selected exposure variables recorded in the datasets collected by *Growing Up in New Zealand,* and outcome variables derived either from those same datasets or from linked national administrative health datasets. Because subsequent chapters of this thesis are presented as research papers suitable for publication in academic journals, the Methods section of each chapter is necessarily brief. This chapter therefore provides a general overview of the methods and describes additional methodological steps with regard to: the linkage of datasets, including national administrative and biological sample datasets; the derivation of variables; and the exploratory data analyses used to determine how to best to manage the longitudinal data. In the excerpts of SAS code used in this chapter, variables and datasets have been renamed for ease of comprehension. As the methods described in this chapter are intended to be supplemental in nature, in some cases reference will be made to the Methods section of a later chapter.

3.1 GROWING UP IN NEW ZEALAND DATASETS

Growing Up in New Zealand has collected interview data at a number of defined data collection waves. During each data collection wave, trained interviewers visited the participant families and conducted face-to-face computer-assisted interviews. The major data collection waves occurred in the antenatal period, and at 9 months, and 2 and 4½ years of child age. During each of these data collection waves, separate datasets were created for the primary caregiver (most often the mother), their partner, and the child (with questions answered by the primary caregiver). Additional smaller datasets were created based on telephone interviews conducted at 23 and 31 months of child age. The 16 GUINZ datasets that were used in the projects described in this thesis were:

- Antenatal mother
- Antenatal partner
- Perinatal hospitalisation linked external data
- 9-month primary caregiver

- 9-month partner
- 9-month child proxy
- National Immunisation Register linked external data (at 1 year of age)
- 23-month primary caregiver telephone interview
- 23-month household grid (household occupancy data)
- 2-year primary caregiver
- 2-year partner
- 2-year child proxy
- 31-month primary caregiver phone call
- 4½-year primary caregiver
- 4½-year child proxy
- 4½-year NZDep2013 linkage

3.1.1 Linkage of Growing Up in New Zealand datasets

Each *Growing Up in New Zealand* dataset in the list above included one or more participant identification variables. These variables consisted of a five-digit family identification number, with a one-digit suffix identifying the individual family member as the primary caregiver, their partner, or the child. Using PROC SORT followed by the MERGE data step in SAS version 9.4 (SAS Institute, Cary, NC, USA), all primary caregiver datasets were initially merged using the primary caregiver identification number, partner datasets were merged using the partner identification number, and child datasets were merged using the child identification number. The resulting datasets were then merged using the overarching family identification number. Merging was performed using the syntax below. The "`IF A=1 and B=1;`" term in the DATA step was used situationally depending on whether the intention was to exclude mismatched records or not.

```
PROC SORT DATA = dataset_A;  BY child_ID;  RUN;
PROC SORT DATA = dataset_B;  BY child_ID;  RUN;
```

```
DATA dataset_C;  MERGE dataset_A (in=A) dataset_B (in=B);
BY child_ID;  IF A=1 and B=1;  RUN;
```

3.1.2 Derivation of new variables from Growing Up in New Zealand data

A number of derived variables (for example, a simplified household crowding index) had been created by GUINZ data managers using data collected during the early data collection waves. However, derived variables were not available for later data collection waves, including the datasets collected at 4½ years of child age, which were used extensively in this thesis. In addition, some variables had not been derived from earlier datasets. For example, the NZiDep, an individualised measure of socioeconomic deprivation, had not been calculated, despite collection of the relevant data at 9 months, and at 4½ years, of child age. While all the GUINZ variables used in the projects described in this thesis required some reformatting or categorisation, the following variables required more extensive work as they had to be derived from raw data before use:

- Broad ethnic group – total response
- Total duration of breastfeeding
- Household smoke exposure
- Household heating modality
- Child's bedroom heating modality
- Primary caregiver NZiDep
- Household crowding index
- Healthcare access
- Primary caregiver experience of racism in a healthcare setting

The following SAS code is an example of how a desired variable, in this case the NZiDep at 9 months of child age, was derived from raw data variables:

```
DATA dataset_A;
SET dataset_A;
IF raw_9m_q1 = 1 THEN nzidep_9m_q1 = 1;
IF raw_9m_q1 = 2 THEN nzidep_9m_q1 = 0;
IF raw_9m_q1 = . THEN nzidep_9m_q1 = .;
IF raw_9m_q2 = 1 THEN nzidep_9m_q4 = 1;
IF raw_9m_q2 = 2 THEN nzidep_9m_q4 = 0;
IF raw_9m_q2 = . THEN nzidep_9m_q4 = .;
IF raw_9m_q3 = 1 THEN nzidep_9m_q5 = 1;
IF raw_9m_q3 = 2 THEN nzidep_9m_q5 = 0;
IF raw_9m_q3 = . THEN nzidep_9m_q5 = .;
IF raw_9m_q4 = 1 THEN nzidep_9m_q6 = 1;
IF raw_9m_q4 = 2 THEN nzidep_9m_q6 = 0;
IF raw_9m_q4 = . THEN nzidep_9m_q6 = .;
IF raw_9m_q5 = 1 THEN nzidep_9m_q7 = 1;
IF raw_9m_q5 = 2 THEN nzidep_9m_q7 = 0;
IF raw_9m_q5 = . THEN nzidep_9m_q7 = .;
IF raw_9m_q6 = 1 THEN nzidep_9m_q8 = 1;
IF raw_9m_q6 = 2 THEN nzidep_9m_q8 = 0;
IF raw_9m_q6 = . THEN nzidep_9m_q8 = .;
IF work_1_9m = 1 THEN nzidep_9m_q2 = 0;

IF work_1_9m = 2 AND OC15_M9M = 1 THEN nzidep_9m_q2 = 1;
IF work_1_9m = 2 AND work_2_9m = 1 THEN nzidep_9m_q2 = 1;
IF work_1_9m = 2 AND work_3_9m = 1 THEN nzidep_9m_q2 = 1;
IF work_1_9m = 2 AND work_4A_9m = 1 THEN nzidep_9m_q2 = 1;
IF work_1_9m = 2 AND work_4B_9m = 1 THEN nzidep_9m_q2 = 1;
IF work_1_9m = 2 AND work_4C_9m = 1 THEN nzidep_9m_q2 = 1;
IF work_1_9m = 2 AND work_4D_9m = 1 THEN nzidep_9m_q2 = 1;
IF work_1_9m = 2 AND work_4E_9m = 1 THEN nzidep_9m_q2 = 1;
IF work_1_9m = 2 AND work_4F_9m = 1 THEN nzidep_9m_q2 = 1;
IF work_1_9m = 2 AND work_4G_9m = 1 THEN nzidep9m_q2 = 1;
IF work_1_9m = 2 AND work_4H_9m = 1 AND new_emp_9m = 1 THEN
nzidep_9m_q2 = 0;
IF work_1_9m = 2 AND work_4H_9m = 1 AND new_emp_9m = 2 THEN
nzidep_9m_q2 = 1;
IF work_1_9m = 2 AND work_4I_9m = 1 THEN nzidep_9m_q2 = 0;
IF work_1_9m = 2 AND work_4J_9m = 1 THEN nzidep_9m_q2 = 0;
IF work_1_9m = 2 AND work_4K_9m = 1 THEN nzidep_9m_q2 = 0;
IF work_1_9m = . AND work_4L_9m = 1 THEN nzidep_9m_q2 = 0;
IF work_5_9m = 96 THEN nzidep_9m_q2 = 0;

nzidep_9m_q3 = 0;
IF benefit_A_9m = 1 THEN nzidep_9m_q3 = 1;
IF benefit_B_9m = 1 THEN nzidep_9m_q3 = 1;
IF benefit_C_9m = 1 THEN nzidep_9m_q3 = 1;
IF benefit_D_9m = 1 THEN nzidep_9m_q3 = 1;

nzidep_score_9m = 0;
IF nzidep9m_q1 = 1 THEN nzidep_score_9m = nzidep_score_9m + 1;
IF nzidep9m_q2 = 1 THEN nzidep_score_9m = nzidep_score_9m + 1;
IF nzidep9m_q3 = 1 THEN nzidep_score_9m = nzidep_score_9m + 1;
IF nzidep9m_q4 = 1 THEN nzidep_score_9m = nzidep_score_9m + 1;
IF nzidep9m_q5 = 1 THEN nzidep_score_9m = nzidep_score_9m + 1;
IF nzidep9m_q6 = 1 THEN nzidep_score_9m = nzidep_score_9m + 1;
IF nzidep9m_q7 = 1 THEN nzidep_score_9m = nzidep_score_9m + 1;
```

```
IF nzidep9m_q8 = 1 THEN nzidep_score_9m = nzidep_score_9m + 1;

IF nzidep_score_9m = 0 THEN nzidep_9m = 1;
IF nzidep_score_9m = 1 THEN nzidep_9m = 2;
IF nzidep_score_9m = 2 THEN nzidep_9m = 3;
IF nzidep_score_9m = 3 THEN nzidep_9m = 4;
IF nzidep_score_9m = 4 THEN nzidep_9m = 4;
IF nzidep_score_9m >=5 THEN nzidep_9m = 5;

RUN;
```

3.1.3 Managing longitudinal data – exploratory data analysis

GUINZ has collected comparable variables at multiple data collection waves. For example, data from which the simplified household crowding index (ratio of occupants to bedrooms) could be calculated were collected in the antenatal interview, the interviews at 9 months and 4½ years, and the telephone interview at 23 months of child age. The best way to manage the longitudinal nature of this data was not immediately clear. In addition, while data on each variable at cross-sectional time points was available, no information was available about the variable of interest during the periods between observations. While a child exposed to living in a crowded home at 9 months and 23 months was likely to have been similarly exposed in the period between these time points, this cannot be inferred with certainty, so a duration of exposure cannot be assumed. Therefore, exposure at the cross-sectional time points must be used directly in some form. Various options for doing so exist:

1) The difficulties of dealing with longitudinal data can be ignored by only working with data collected at a single cross-sectional time point. This is simple to do and may be appropriate where the exposure is expected to be stable across time, e.g. biological sex, or where the exposure must be accounted for in a multivariable model but is not the main exposure of interest for the study. This approach has been taken in Chapters 4, 5, 8, 9, and 10 as these projects were intentionally kept simple with a minimal number of exposure variables.

2) Exposure to the same variable at multiple time points can be treated as exposure to multiple independent variables. This might be appropriate in some circumstances, e.g. if an exposure in early childhood is hypothesised to have a different effect on the outcome than exposure at later times. However, in general, exposures to the same

variables at different time points are likely to be statistically correlated leading to problems with regression models.

3) Exposure to the same variable at multiple time points can be treated as additive exposure. For example, exposure to household crowding at 9 months, 23 months and 4½ years can be added up to generate a score between 0 (never exposed) and 3 (exposed at all three time points). This would be appropriate where exposure at different time points was expected to have a similar effect and the total duration of exposure (which can't be calculated itself) was expected to be correlated with the outcome.

4) Exposure to the same variable at multiple time points can be collapsed to a binary ever exposed vs. never exposed variable. This makes analysis very simple, particularly if multiple such variables are to be included in a regression model. However, much of the detail is necessarily lost, which could be a problem if the collapsed variable was of interest in that research project. This approach has been taken in Chapters 6 and 7, as the intention was to examine a small number of exposures in detail (ethnicity and healthcare access) while correcting for a wide range of other exposures.

5) Exposure to the same variable at multiple time points can be managed by creating a series of variables representing various permutations of exposure at different times. For a binary variable measured twice, this is effectively a 2x2 cross tabulation that yields 4 variables. For variables with a greater number of levels and/or more frequent measurements, the number of resulting variables grows exponentially. For example, exposure to household crowding (a binary variable) at three time points would lead to the creation of 8 variables: never exposed; exposed at all three time points; exposed at 9 months; exposed at 23 months; exposed at 4½ years; exposed at 9 months and 23 months; exposed at 9 months and 4½ years; exposed at 23 months and 4½ years. This might be appropriate where the variable in question is of particular interest but clearly yields a large number of variables which in turn creates concerns regarding loss of statistical power and over-fitting of multivariable models.

To demonstrate how these methods of managing longitudinal data work, **Figure 1** shows the odds ratio estimates and 95% confidence intervals for logistic regression analyses using the methods described above. In each case, the only exposure variable is household crowding and the outcome variable is admission to hospital for an infectious disease in the first five years of life (treated as a binary variable). In this example the cross sectional, binary and cumulative methods all yielded similar effect estimates.

3.2 LINKAGE TO ADMINISTRATIVE HEALTH DATA

At the interview conducted at 4½ years of child age, informed consent was sought from each primary caregiver to access their child's routinely collected administrative health data. For the projects included in this thesis, the administrative data that were utilised included hospital discharge records stored within the National Minimum Dataset (NMDS) (41), and community pharmacy dispensing records stored within the Pharmaceutical Collection (52). Chapter 6 also includes linked data from perinatal hospital records and the National Immunisation Register (NIR), which consists of records of scheduled immunisations received. These perinatal and NIR datasets had previously been obtained by colleagues at GUINZ and were available to internal users in a cleaned form, with the child ID number attached, and with derived variables (for example immunisation timeliness) included. For the projects in this thesis, the NMDS and Pharmaceutical Collection datasets were obtained from the NZ Ministry of Health. This involved liaising with staff at the Ministry to establish a contract for this process, then providing a list of National Health Index (NHI) numbers and identifying data (name, sex, date of birth, address) to the Ministry for those children whose primary caregiver had consented to linkage. The datasets were then provided as spreadsheets in the comma-separated values (*.csv*) format.

3.2.1 National Health Index numbers

The NHI number is a three-letter, four-digit alphanumeric code in the format ABC1234. The assignment of an NHI number can be initiated at any health contact – this can occur at birth if the child is born in hospital, or later on attendance at a family doctor or hospital emergency department. While each NHI number is unique to a given individual, it is possible for an individual to be inadvertently assigned more than one NHI number. For a child this can happen if different demographic data are provided on different occasions when attending hospital – often when relatives provide variations of the child's name or other demographic details, or if there have been changes of address. A new NHI number also can be assigned if a person is brought to hospital unable to communicate and their identity cannot be established. Sometimes these new NHIs are able to be merged during the hospital stay; otherwise the Ministry of Health attempts to link such secondary NHIs with the individual's primary NHI number at an administrative level. If numerous health contacts have occurred using an NHI

other than that assigned at birth, it is possible for the birth NHI to be designated as the secondary NHI.

GUINZ obtained birth NHIs from hospital perinatal records for children whose primary caregiver consented to this. For the small number of children whose primary caregiver did not consent to linkage in the perinatal period or at 1 year of age, but later consented for linkage at 4½ years of child age, family were asked to provide NHI numbers as documented in prescriptions or hospital discharge paperwork for the child. Unfortunately this led to the potential for inaccurate recording of NHIs for these children.

3.2.2 Structure of the National Minimum Dataset

The NMDS was provided in the form of a single long-form list with one row per hospital admission and the potential for multiple rows per child if they had multiple admissions. The dataset consisted of 14217 rows of data, and each row consisted of 107 variables related to that hospital admission. These variables included demographic and identifying data such as the GUINZ NHI number of record, the primary NHI number as recorded by the Ministry, and the NHI number used during that hospital admission event, as well as date of birth, sex, and ethnicity as recorded in the NHI system. They also included clinical data such as hospital admission and discharge dates, hospitalisation type (e.g. birth, acute inpatient, elective), and up to 20 discharge diagnostic codes, coded using the Australian Modification of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10-AM). A large number of variables were provided that were not used for the projects in this thesis, such as accident codes and surgical operation codes and dates.

3.2.3 Data management and cleaning of the National Minimum Dataset

The NMDS was imported into SAS version 9.4 for data management and cleaning. As a first step duplicate records were removed using PROC SORT:

```
PROC SORT DATA = dataset_A noduplicates;  BY _all_;  RUN;
```

Basic GUINZ demographic data (date of birth, sex) was then attached to each NMDS record by merging using the supplied NHI number. The NHI numbers and demographic data were

compared between the NMDS and GUINZ datasets. Mismatches in NHI number, sex, and/or date of birth were manually reviewed to confirm that the NMDS data pertained to the correct individual. Single-digit discrepancies in date of birth were considered to be minor typographical errors and did not lead to removal of the record. Similarly, a mismatch in recorded sex during a single admission was also considered a typographical error where other admissions matched the sex recorded by GUINZ. Mismatch of NHI numbers was considered acceptable where the GUINZ NHI of record was listed as a secondary NHI for that admission in the NMDS, or where a clear link could be established between the GUINZ NHI of record and the primary NHI for the admission using a third NHI. Where a mismatch in date of birth or sex could not be attributed to typographical error, these NHIs were considered inaccurate and admissions associated with these NHIs were excluded. NHIs that had community pharmaceutical dispensing records in the Pharmaceutical Collection dated prior to the GUINZ date of birth were considered inaccurate and all admissions associated with such NHIs were removed from the NMDS. Likewise, NHIs determined to be inaccurate during cleaning of the NMDS were removed from the Pharmaceutical Collection.

Once the dataset was cleaned, further steps were required to identify hospital admissions for infectious diseases in general, and for skin and soft tissue infections specifically. As the intention was to capture community-onset infections in the first five years of life, admissions outside this scope were excluded in several ways. Admissions were excluded if they had an admission type of 'BT' indicating a birth admission, an admitting service of obstetrics or neonatal intensive care, or an ICD-10-AM diagnostic code indicating that the child had been born during that admission (e.g. Z380 for a singleton liveborn infant born in hospital). Admissions were excluded if the child was over five years of age at the time the admission event started. Admissions for non-medical reasons were also excluded after being identified using relevant diagnostic codes, e.g. Z762 for "health supervision and care of other healthy infant and child" (used to identify an infant rooming-in with an unwell mother). Admissions for infectious disease, or for skin infection, were identified using arrays in SAS with the syntax shown below. For Chapter 6, the intention was to detect hospitalisations for community-onset infection where the infection was the main reason for hospital attendance. Therefore, only the first diagnostic code, representing the primary illness addressed during that hospitalisation, was used as in the first example below. In Chapter 7, where the intention was to detect all skin infections managed in hospital, all diagnostic codes were used as in the second example below.

```
DATA dataset_A;
SET dataset_A;
ARRAY xx1[*] DIAG01;
respiratory_ID_Dx = 0;
DO i = 1 TO Dim(xx1);
IF (xx1[i] IN ("A360", "A361", … , "J860", "J869"))
THEN respiratory_ID_Dx = respiratory_ID_Dx + 1;
END;
DROP i;
RUN;

DATA dataset_A;
SET dataset_A;
ARRAY xx1[*] DIAG01 - DIAG20;
ssti_ID_any_Dx = 0;
DO i = 1 TO Dim(xx1);
IF (xx1[i] IN ("H050", "H602", … "L309", "L303"))
THEN ssti_ID_any_Dx = 1;
END;
DROP i;
RUN;
```

Once infectious disease hospitalisations had been identified, PROC SUMMARY was used to add up the number of hospitalisations per child in total, in each year of life, and in each subtype of infectious disease (respiratory, gastrointestinal/abdominal, genitourinary, skin and soft tissue, and other). The dataset generated by the PROC SUMMARY procedure was then merged with the combined GUINZ dataset using the child ID number. The syntax of the PROC SUMMARY procedure is given below; the "…" indicates that other variables were also be summarised but have not been shown for clarity.

```
PROC SUMMARY DATA = dataset_A NWAY MISSING;
CLASS nhi_number;
VAR respiratory_ID_Dx … ;
OUTPUT OUT = ID_Dx_summary (drop=_:)
            SUM(respiratory_ID_Dx) = resp_ID_Dx_sum
… ;
      RUN;
```

3.2.4 Structure of the Pharmaceutical Collection

The Pharmaceutical Collection was provided in the form of two long-form lists – a dispensing record list and a medication name and formulation list. The dispensing record list contained 277219 rows with multiple rows per child. Each row contained 25 variables including the supplied, primary and event NHI numbers (as described for the NMDS above) as well as basic

demographic data, the date of dispensing, the amount prescribed and dispensed (either in days of treatment, number of tablets, or volume of liquid medication), and a "key" – a 5-digit numeric code specific to the formulation of the medication dispensed. The second list consisted of these key codes with the corresponding medication name and formulation data, as well as three therapeutic group levels with increasing focus. For example, there were several codes for various formulations of amoxicillin (intravenous, oral capsules and varied concentrations of oral liquid), all of which would fall under "Infections - Agents for Systemic Use" (level 1), "Antibacterials" (level 2), and "Penicillins" (level 3). The two lists were merged using the key code so that each dispensing record now included the medication name and these therapeutic group levels.

3.2.5 Data management and cleaning of the Pharmaceutical Collection

As with the NMDS, the Pharmaceutical Collection required cleaning to remove records with inaccurate NHI numbers. NHI numbers were deemed to be inaccurate if dispensing records from prior to the child's date of birth were recorded in the Pharmaceutical Collection, or if that NHI was associated with mismatches in demographic details between the NMDS and the GUINZ datasets that could not be attributed to typographic error. The demographic data included in the Pharmaceutical Collection was not sufficient to allow exclusion of records or NHI numbers.

Individual dispensing records were removed if the date of dispensing and date of birth indicated that the child was over the age of 5 when the medication was dispensed, if the key code was listed as zero or missing, or if the dispensing was of a 'repeat' prescription (3-month prescriptions for long-term medications are often dispensed as monthly 'repeats' – this is not often done with short-term medications like antibiotics). Once these dispensing records had been excluded, records were further limited to those for medications falling into the level 2 therapeutic groups of "Antibacterials" and "Urinary Tract Infections".

After attaching a code for the antibiotic classes of interest and calculating child age at the time of each dispensing record, the PROC SUMMARY procedure was again used to collate summary statistics for the number of courses of antibiotic dispensed per child in total, and by

drug class and year of life. The resulting datasets were merged with each other, then with the GUINZ datasets.

3.3 GROWING UP IN NEW ZEALAND BIOLOGICAL SAMPLE DATA

Consent to collect biological samples was sought at the interview conducted at 4½ years of child age. For those children whose caregiver consented, buccal swabs were collected to obtain host DNA, and anterior nares, oropharyngeal and antecubital fossa skin swabs were collected for bacterial culture. Due to variable child cooperation with swab collection, not all children had all three culture swabs collected. These swabs were transported to LabTests, a large community laboratory in Auckland, New Zealand, for culture and identification of *Staphylococcus aureus* and *Streptococcus pyogenes*. The details of the culture media and identification processes used are documented in the Methods sections of Chapters 7, 8, 9, and 10. Isolates of *S. aureus* and *S. pyogenes* were stored for subsequent genetic testing. The original swabs were also stored for possible future microbiome testing. The genotyping work described below was funded by a grant-in-aid from the Maurice and Phyllis Paykel Trust (Auckland, NZ).

LabTests provided the results of bacterial culture in the form of a spreadsheet. This spreadsheet consisted of a long-form list of the culture results for a maximum of three swabs per child – one from each site. Each swab result row in the spreadsheet included the GUINZ child ID, data about the timing of collection, the anatomical site swabbed, and the presence or absence of *S. aureus* and *S. pyogenes*. Antibiotic susceptibility results for cefoxitin (to detect methicillin resistance), erythromycin, and trimethoprim-sulfamethoxazole were provided for isolates of *S. aureus*.

3.3.1 Data management and cleaning of the Growing Up in New Zealand biological sample data

This dataset required minimal cleaning other than the removal of swabs collected from the 'leading light' test cohort and swabs provided by GUINZ staff to test the collection and laboratory processes. Once the desired variables had been identified, the PROC TRANSPOSE

procedure was used to create multiple single-variable, wide-form datasets for each variable based on the swab site. These datasets were then merged together to create a wide-form list of swab results for each child. The TRANSPOSE procedure had to be performed multiple times, once for each desired variable, using the following syntax (with *S. aureus* isolation used as an example):

```
PROC SUMMARY DATA = swab_long_1 NWAY MISSING;
CLASS child_ID swab_site;
VAR staph;
OUTPUT OUT = swab_long_2 (DROP=_:) MAX=;
RUN;

PROC TRANSPOSE DATA = swab_long_2 OUT = staph_wide PREFIX = staph_;
BY child_ID;
ID swab_site;
VAR staph;
RUN;
```

Each iteration of the PROC TRANSPOSE procedure uses data from the source dataset (in this example, swab_long_2) to output a new dataset (in this example, “staph_wide”). The new dataset will be in a wide format with one row for each “child_ID” and three desired variables, “staph_nasal”, “staph_throat”, and “staph_skin”, with names generated using the specified prefix “staph_” and the value recorded in the variable “swab_site” (nasal, throat or skin) and values (in this case a binary 1 or 0) taken from the value of the variable “staph” in the source dataset. The PROC TRANSPOSE procedure is repeated for other desired variables, such as isolation of *S. pyogenes*, with each desired variable being transposed into a separate dataset. These datasets can then be merged using the child ID variable:

```
DATA swab_wide;  MERGE … staph_wide strep_wide … ;
BY child_ID;  RUN;
```

Once merged into a single wide-form list, the swab data could be merged with the other GUINZ datasets for analysis in Chapters 7, 8, 9, and 10.

3.3.2 Staphylococcus aureus genotyping

There are two main methods for typing *S. aureus* in current use – *spa*-typing and whole genome sequencing. Whole genome sequencing looks at single nucleotide polymorphisms

across the core genome and is able to determine lineages very precisely. However, it remains expensive – prohibitively so for the projects included in this thesis. The most cost effective alternative is s*pa*-typing, which also discriminates strains well. As *spa*-typing involves sequencing of a single gene, it is relatively inexpensive, and the laboratory work and bioinformatics relatively simple, when compared with whole genome sequencing.

Spa-typing involves sequencing the polymorphic region of the staphylococcal protein A (*spa*) gene (44, 45). Protein A released by *S. aureus* binds the heavy chain of immunoglobulin G, interfering with humoral immunity and opsonisation. The polymorphic region includes a sequence of one or more Variable Number Tandem Repeats (VNTRs), each repeat being 21 to 27 base pairs in length (typically 24, i.e. 8 codons). These VNTRs are subject to mutation both in the form of single base pair changes – insertions, deletions and substitutions – and of duplications, excisions, and relocations of whole repeat sequences. While standard DNA alignment techniques manage single base pair changes well, they are not equipped to manage DNA sequence changes at the level of whole repeats as they assign an excessively high cost to these events. The Based Upon Repeat Pattern (BURP) algorithm can account for both single base pair changes as well as the duplication, excision, or relocation of whole repeat sequences in any order, and assigns a lower cost to these whole repeat changes than do standard alignment techniques (147). The *spa* clonal complexes derived by use of the BURP algorithm have been shown to have a high degree of concordance with sequence types assigned using Multilocus Sequence Typing (MLST) when clustering is performed using the default parameters (i.e. when restricted to *spa*-types with 5 or more repeats and using a cost distance of 4). Shorter repeat sequences have inadequate information content to infer evolutionary relationships but this must be balanced against excluding an excessive number of *spa*-types with short repeat sequences.

3.3.3 Streptococcus pyogenes genotyping

The most cost-effective method for genotyping *S. pyogenes* in current use is *emm*-typing – sequencing of the *emm* gene coding for the cell surface M-protein. As with protein A for *S. aureus*, M-protein is a virulence factor for *S. pyogenes* which acts to prevent opsonisation, complement fixation, and phagocytosis. The M-protein can be used for serotyping, and *emm*-typing involves sequencing the hypervariable part of the gene which determines the M

serotype. The first 180 bases (of which 150 are the discriminative coding portion) of the *emm* hypervariable region are sequenced and compared with known strain sequences.

3.3.4 Bacterial culture methods for genotyping

As described in Chapters 7, 8, 9, and 10, isolates of *S. aureus* and *S. pyogenes* were stored for 58.8% of children colonised with S. aureus, and 36.1% of children colonised with S. pyogenes. These isolates were obtained from -80^{O}C storage and plated onto agar. For *S. aureus*, sheep's blood agar was used initially, before changing to mannitol-salt agar, a selective medium for *S. aureus*, to facilitate the identification process. Sheep's blood agar was used to culture *S. pyogenes*.

3.3.5 Staphylococcus aureus spa-gene PCR

To perform PCR amplification of the *spa* gene to genotype *S. aureus*, colonies of *S. aureus* were suspended in 100 µL of sterile water to which 1 µL of 1 mg/mL lysostaphin was added (lysostaphin from *Staphylococcus staphylolyticus*, Sigma-Aldrich). The isolates were incubated in the lysostaphin solution at 37^{O}C for 30 minutes in a water bath. The lysostaphin was then inactivated by heating to 100°C for 10 minutes in a heater block. The sample was then placed in a centrifuge at 13,000 RPM for 3 minutes. The resulting supernatant was then used as the template DNA for the polymerase chain reaction (PCR) process.

The *spa* PCR master mix was made using the following proportions for a total volume of 48 µL per sample well:

- 36.8 µL water
- 5 µL 10x PCR buffer
- 3 µL magnesium chloride
- 1 µL *spa* Forward primer (5'-TAAAGACGATCCTTCRGTGAGC-3')
- 1 µL *spa* Reverse primer (5'-CAGCAGTAGTGCCGTTTGCT-3')
- 1 µL dNTPs

- 0.2 µL *taq* polymerase

In each well of a 96-well plate, 2 µL of template DNA was added to the 48 µL of PCR master mix. The PCR amplification was then performed using the following settings:

- 3 minutes at 95°C
- 30 cycles of:
- 30 seconds at 95°C
- 30 seconds at 56°C
- 30 seconds at 72°C
- 5 minutes at 72°C
- Hold at 10°C

Successful amplification was confirmed by running a sample of the PCR products from each 96-well plate on an agarose gel. **Figure 2** demonstrates the appearance of the gel after a successful PCR run.

3.3.6 Streptococcus pyogenes emm-gene PCR

A specific DNA extraction step was not required for *S. pyogenes*. Instead, a tiny amount of material from a colony of *S. pyogenes* was picked up with a wire loop and added directly to the *emm*-gene PCR master mix. Lysis was then achieved by heating in the PCR machine as the initial step of the PCR reaction. The *emm* PCR master mix was made using the follow proportions for a total volume of 25 µL per sample well:

- 19.32 µL water
- 2.5 µL 10x PCR buffer
- 1.5 µL magnesium chloride
- 0.5 µL *emm* Forward primer (5'-TATTSGCTTAGAAAATTAA-3')

- 0.5 µL *emm* Reverse primer (5'-GCAAGTTCTTCAGCTTGTTT-3')
- 0.5 µL dNTPs
- 0.18 µL *taq* polymerase

PCR amplification was then performed using the following settings:

- 5 minutes at 95°C
- 30 cycles of:
- 15 seconds at 94°C
- 30 seconds at 47°C
- 1 minute 15 seconds at 72°C
- 10 minutes at 72°C
- Hold at 4°C

Successful amplification was again confirmed using agarose gel electrophoresis.

3.3.7 Sequencing and genotyping of spa and emm gene PCR products

Once successful amplification had been confirmed, the 96-well PCR plates were packaged according to IATA standards and sent by courier to Macrogen Inc. (Seoul, Korea) for sequencing. Both forward and reverse sequences were requested. The results of sequencing were provided in several electronic formats, including the AB1 format which was used to upload results for genotyping.

For *S. aureus*, sequences were uploaded into the Ridom StaphType programme (148). StaphType automatically determines the consensus sequence in most cases, and then assigns sequences to a *spa*-type where possible. StaphType also provides an assessment of the quality of the match between the uploaded sequence and the reference sequence for the best-match

spa-type. Sequences for which the quality assessment was less than excellent were manually reviewed and edited or repaired where necessary. Sequencing failures were identified so that repeat PCR and sequencing could be performed. One novel *spa*-type was identified and the sequence uploaded to the Ridom SpaServer. Once *spa*-types had been assigned, the Based Upon Repeat Pattern (BURP) algorithm contained within the StaphType programme was used to cluster the *spa*-types into *spa* clonal complexes.

For *S. pyogenes*, sequences were uploaded into Geneious (Biomatters, Ltd. Auckland, NZ). A consensus sequence was constructed using the forward and reverse sequences. The consensus sequence was then used to determine the *emm*-type by comparing with known *emm*-type sequences using the Nucleotide BLAST (Basic Local Alignment Search Tool) web tool available online from the National Center for Biotechnology Information (U.S. National Library of Medicine, National Institutes of Health, U.S.A., https://blast.ncbi.nlm.nih.gov/Blast.cgi).

3.3.8 Data management for bacterial genotypic data

Once the *spa* or *emm* type had been determined for each stored isolate, this result (and for *S. aureus*, an additional separate dataset containing the *spa* clonal complex data) was imported into SAS. Then, through a series of DATA steps, these genotype datasets were merged with the long-form swab result list. This meant that the genotype result was now associated with both an individual child and the anatomical site sampled. Following this, a wide-form dataset was created using the same approach as described previously – a series of PROC TRANSPOSE steps followed by merging the resulting datasets.

3.4 FIGURES

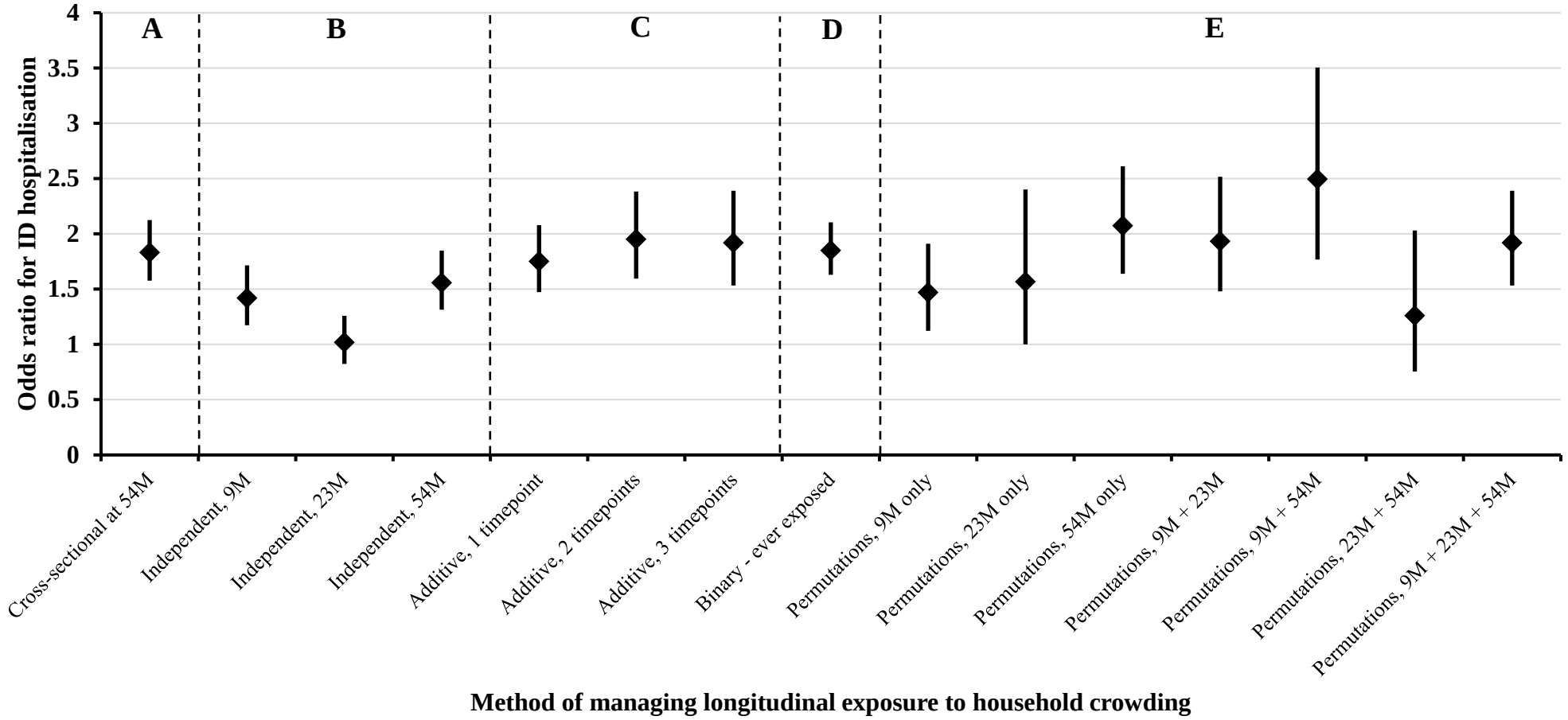
A
B
C
D
E
Odds ratio for ID hospitalisation
4
3.5
3
2.5
2
1.5
1
0.5
0
Cross-sectional at 54M
Independent, 9M
Independent, 23M
Independent, 54M
Additive, 1 timepoint
Additive, 2 timepoints
Additive, 3 timepoints
Binary - ever exposed
Permutations, 9M only
Permutations, 23M only
Permutations, 54M only
Permutations, 9M + 23M
Permutations, 9M + 54M
Permutations, 23M + 54M
Permutations, 9M + 23M + 54M
Method of managing longitudinal exposure to household crowding

Figure 1: Odds ratios for the association with hospitalisation with an infectious disease before the age of five years generated using five methods of managing longitudinal exposure to household crowding

Figure 1 footnote: A) using cross-sectional exposure at 54 months only; B) treating exposure at different timepoints as independent variables; C) treating exposure at one, two, or three timepoints in an additive fashion; D) categorizing exposure as ever vs. never exposed; and, E) categorizing based on various permutations of exposure at the three measured time points.

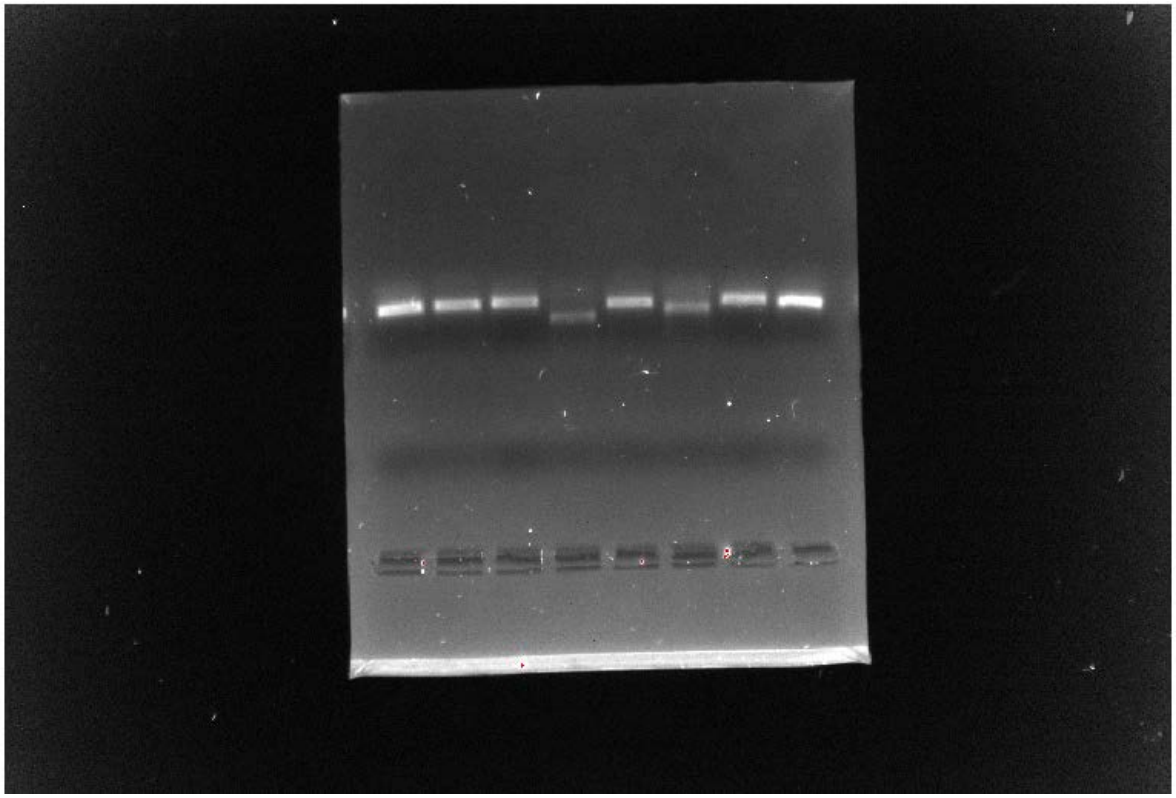

Figure 2: Image of agarose gel electrophoresis of *spa* gene PCR product stained with SYBR-Safe (Invitrogen, Thermo-Fisher Scientific).

CHAPTER 4: HOW DIFFERING METHODS OF ASCRIBING ETHNICITY AND SOCIOECONOMIC STATUS AFFECT RISK ESTIMATES FOR HOSPITALISATION WITH INFECTIOUS DISEASE

The major focus of this thesis is to examine differences in health outcomes between children of differing ethnic and socioeconomic backgrounds; thus, it is important that validated methods of defining ethnic group membership and socioeconomic deprivation are used. This chapter provides that validation by comparing three methods of ascribing ethnicity – self-prioritisation to a single ethnicity (in this case by the primary caregiver of the cohort child), total response ethnicity, and single-combined ethnicity – and three methods of describing socioeconomic deprivation – household income, the census-derived NZDep2013, and the survey-derived NZiDep.

Ascribing ethnicity is complex, and none of the methods examined were perfect. In subsequent chapters of this thesis, the self-prioritised method of ascribing ethnicity will be used as this method was found to be the simplest and preserved subgroup size while differentiating risk between broad ethnic groups. The main weaknesses of the self-prioritised method are that the diversity of risk within broad ethnic groups was obscured and some participants had to be externally prioritised as they listed more than one ethnicity or declined to answer the question. Household income proved difficult to use due to missing data and subsequent chapters will use NZDep2013 (Chapter 5) or NZiDep (all other chapters) depending on which covariates are to be examined in combination with deprivation.

This chapter intentionally looked at ethnicity and socioeconomic deprivation only and did not include the large amount of data Growing Up in New Zealand has collected on other social determinants of health such as household transience and crowding, access to healthcare, and exposure to racism. It is also cross sectional, using only data collected at 4½ years of child age and not from prior data collection waves. Greater detail on the social determinants of health and exposures earlier in childhood will be included in Chapter 6.

The research described in this chapter has been published in *Epidemiology & Infection*:

Hobbs MR, Atatoa Carr P, Fa'alili-Fidow J, Pillai A, Morton SMB, Grant CC. How differing methods of ascribing ethnicity and socio-economic status affect risk estimates for hospitalisation with infectious disease. *Epidemiology & Infection*. 2018;147(e40):1-9.

4.1 INTRODUCTION

The epidemiology of infectious disease (ID) in New Zealand (NZ) is marked by significant ethnic and socioeconomic disparities, with higher rates observed in Māori and Pacific peoples, and in areas of greater socioeconomic deprivation (1, 3, 8). Likewise, higher rates of ID are also seen in indigenous and marginalised ethnic minority groups in comparable developed countries such as Australia and the United States (9, 11). Therefore accurate measures of ethnic identity and socioeconomic deprivation are of particular importance in epidemiological research.

Ethnicity is a complicated social construct that describes cultural identity or affiliation (149). The related but distinct concept of race is not generally used in research in NZ. There are a number of methods of ascribing ethnicity in epidemiological research including self-prioritisation, total response, and single-combined ethnicity, each method having its advantages and disadvantages (150). Socioeconomic deprivation can also be measured in various ways, including by directly questioning household income, and by using census-derived geographic measures (47) or survey-derived individual measures (50).

In this study, we used hospitalisation for an ID before the age of five years, an outcome known to be linked to ethnicity and socioeconomic disadvantage (1), to compare different measures of ethnicity and socioeconomic deprivation.

4.2 METHODS

4.2.1 Study population

This study was conducted within the *Growing Up in New Zealand* (GUINZ) longitudinal birth cohort. GUINZ enrolled 6822 pregnant mothers from the Auckland, Counties-Manukau, and Waikato District Health Board areas due to deliver in 2009-2010 (37, 39). The cohort includes 6853 children born from these pregnancies, 11% of the national birth cohort for the

recruitment period. The cohort is generalisable to the national birth cohort with regards to ethnic and socioeconomic diversity (38).

4.2.2 Ethics

Ethical approval was obtained from the Ministry of Health Northern Y Regional Ethics Committee (NTY/08106/055). Written informed consent for interviews and data linkage was completed by each child's primary caregiver.

4.2.3 Data collection and linkage

This study uses data from a face-to-face interview with the primary caregiver of the study child at 4½ years of child age, with linkage to the National Minimum Dataset (NMDS). The NMDS contains records of all public hospital admissions in NZ, including emergency department visits but not outpatient clinic attendances (41). Public hospital care, including all acute inpatient paediatric care, is free for NZ permanent residents and citizens. The NMDS includes discharge diagnoses coded using the Australian Modification of the International Classification of Diseases and Health Related Problems (ICD-10-AM) (151), with the first code representing the primary health problem managed during the hospitalisation.

4.2.4 Primary outcome

The primary outcome was hospitalisation for an ID in the first 5 years of life, treated as a binary (ever/never) variable. Hospitalisations for an ID were identified using the first diagnostic code listed in the NMDS. Acute and chronic infections were included, as were infective exacerbations of chronic non-infective conditions such as asthma. Hospitalisations for non-infective sequelae of past infections, birth hospitalisations, and hospitalisations for non-medical reasons (e.g. maternal hospitalisation) were excluded. To avoid unnecessary duplication, the list of ICD-10 codes used has been included in **Chapter 6, Table 18,** and is not replicated in this chapter.

4.2.5 Ethnicity variables

Primary caregivers were asked the following questions regarding the ethnicity of the study child:

1. Which ethnic group or groups does (child name) belong to?
2. Which is the MAIN ethnic group that (child name) identifies with?

Multiple responses were allowed for question 1. One, or at most two, responses were allowed for question 2.

Responses were aggregated into broad ethnic groups for the purposes of this study – Māori, Pacific, Asian, and European/Other. Responses of 'New Zealander' (479 children [8.5%]) were included in the European/Other group. None of the methods described below account for multiple ethnicities within an ethnic group.

Self-prioritised ethnicity was defined as the response to question 2 above. If two ethnicities from different ethnic groups were indicated, then for the purposes of this study only these responses were prioritised in the order Māori, Pacific, Asian, European/Other. This resulted in a single ethnic group variable with four non-overlapping levels. ID hospitalisations were compared between these groups and also with those unable to prioritise a single ethnic group excluded. The European/Other group was used as the comparator in these self-prioritised ethnicity analyses.

Total response ethnicity was defined as the response to question 1 above, with membership of each ethnic group recorded separately. This resulted in four overlapping binary ethnic group variables. In unadjusted analyses, ID hospitalisations for a given ethnic group were compared with the combined pool of children not in that group, e.g. Māori children were compared with all non-Māori children. All four groups were included in the multivariable analyses. As this approach meant there was no single baseline for comparison, analyses were repeated using the non-overlapping 'European/Other only' group as a comparator.

Single-combined ethnicity was also defined using responses to question 1 with individuals assigned to a single or combination ethnic group matching their combination of ethnicities. This resulted in a single ethnic group variable with fifteen non-overlapping levels. As several combination groups included few individuals, analyses were also presented using a modified approach focussing on Māori and Pacific children, in which mixed ethnicities were aggregated into the following groups: Māori + other non-Pacific ethnicity; Pacific + other non-Māori ethnicity; Māori + Pacific +/- other ethnicity; and European/Other + Asian. The 'European/Other only' ethnic group was used as the comparator in both analyses.

4.2.6 Socioeconomic variables

Household income was queried directly and primary caregivers were able to respond with a weekly, fortnightly, four-weekly, monthly, or annual amount, before or after tax, from which annual income was calculated. Income brackets were offered to participants unable to answer, again before or after tax. NZ has a system of progressive marginal tax rates applied to individual earners, and tax credits which are available for lower income families. For post-tax amounts, it was not possible to calculate the corresponding pre-tax amount as household income may have been spread over several earners, and eligibility for tax credits was not recorded.

The NZDep is a census-derived, area-level measure of deprivation determined for the household using the usual address of the child (47). The NZDep2013 was calculated from 2013 national census responses covering aspects of deprivation including internet access, receipt of government benefits, household income, employment status, educational qualifications, home ownership, family structure, household crowding, and access to a car. An ordinal scale from 1 (least deprived 10%) to 10 (most deprived 10%) is calculated for each census meshblock – an area containing on average 81 people.

The NZiDep is an individualised index of deprivation, calculated for the primary caregiver from responses to eight interview questions regarding unemployment, receipt of government benefits and community charity, and the need to economise on food, heating, and footwear (50). The interview questions, and the standard NZiDep questionnaire, are included in **Table**

1. A score from 1 (no responses suggesting deprivation) to 5 (5 – 8 responses suggesting deprivation) is calculated. Comparisons of ID hospitalisations were performed using the score and a binary variable comparing those scoring 1 and 2 with those scoring 3, 4, and 5.

4.2.7 Statistical analyses

Analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC, U.S.A.). Proportions hospitalised for an ID and risk differences between ethnicity methods were calculated. Unadjusted analyses were presented using relative risks, 95% confidence intervals, and p-values derived from the chi-squared or Fisher's exact tests. Multivariable analyses were performed using log-binomial regression and were presented as adjusted relative risks with 95% confidence intervals. Log-binomial regression was performed in preference to logistic regression as the outcome used was not rare. Multivariable models were first built using only the multiple levels of the variable of interest, then repeated with ethnicity models corrected for socioeconomic deprivation using the NZDep2013 quintiles and socioeconomic models corrected for ethnicity using self-prioritised ethnicity.

4.3 RESULTS

4.3.1 The effect of ethnicity measures on risk of hospitalisation for an ID

A total of 5602 children had results available from both the 4½ year interview and linked hospitalisation data from the NMDS. A single self-prioritised ethnicity was provided for 4991 (89.1%) children, while two were provided for 528 (9.4%) children, 133 (2.4%) within one broad ethnic group and 395 (7.1%) across two ethnic groups. The caregivers of 83 (1.5%) children declined to prioritise an ethnicity. A single total-response ethnicity was identified for 3062 (54.7%) children with the remainder having multiple ethnicities identified. As some of these multiple ethnicities fell within the same broad ethnic group, 3880 (69.3%) children had a single total response ethnic group. A majority of children in each total response ethnic group were self-prioritised to the corresponding group, as shown in **Table 2**.

A total of 1453 (25.9%) children were hospitalised for an ID. **Table 3** shows the relative risk of hospitalisation for an ID for each ethnic group by method of assigning ethnicity. Māori and Pacific children had a greater risk of hospitalisation for an ID across all methods of ascribing ethnicity and this was only partially reduced by correction for socioeconomic deprivation. Relative risk estimates were higher for Māori and Pacific children when self-prioritised ethnicity was used compared with total-response ethnicity. When no fixed comparator group was used, European/Other total response ethnicity was associated with a lower risk of hospitalisation for an ID. Using single-combined ethnicity, the larger groups containing Māori or Pacific children showed an increased risk for hospitalisation with an ID, as did the 'Asian only' group. No significant associations could be identified for the smallest combined ethnicity groups containing less than 100 children. After aggregation, a significant association with hospitalisation for an ID was apparent for all single or combination groups containing children with Māori or Pacific ethnicity. Higher relative risk estimates were seen for the Māori-only, Pacific-only, and Māori + Pacific (+/- other) groups than for the mixed Māori + non-Pacific and Pacific + non-Māori groups.

When risk differences between corresponding ethnic groups using different methods were calculated (**Table 4**), a slightly higher risk for European/Other children and a non-significant trend towards lower risk for Māori and Pacific children were seen when using total response compared with self-prioritised. Self-prioritised Māori ethnicity appeared to overestimate the risk for mixed Māori + non-Pacific children defined using aggregated single-combined ethnicity. Likewise, Pacific self-prioritised ethnicity appeared to overestimate the risk for mixed Pacific + non-Māori children. These differences were further accentuated when comparing total response with single-combined ethnicity. In addition, total response Māori ethnicity was found to underestimate the risk for Māori-only, and mixed Māori + Pacific children, while total response Pacific ethnicity underestimated the risk for Pacific-only children.

4.3.2 The effect of socioeconomic status measures of risk of hospitalisation for an ID

Pre-tax household income was provided by 3833 (68.4%) primary caregivers and post-tax income by 1165 (20.8%). Household income was not provided by 604 (10.8%) primary caregivers. This data was not missing at random – 5.0% of those in the least deprived

NZDep2013 quintile and 21.5% of those in the most deprived NZDep2013 quintile had missing household income data ($p<0.0001$). In addition, post-tax income was provided by 15.0% of those in the least deprived quintile and by 35.0% of those in the most deprived quintile ($p<0.0001$). Due to the risk of bias and the inability to correlate pre- and post-tax income accurately, further analyses were not performed using household income.

While the NZDep2013 resulted in quintiles of similar size (range 952 – 1373), the NZiDep gave 55.1% of primary caregivers a score of 1. Both systems demonstrated a social gradient in relative risk of hospitalisation for an ID that was maintained after correction for ethnicity, as shown in **Table 5**. The full range of NZiDep scores was seen within each NZDep2013 quintile but there was a strong relationship between increasing NZDep2013 quintile and increasing NZiDep score, whether used directly or in a binary form (**Table 6**).

4.3.3 Relationship between ethnicity and socioeconomic status

Examination of socioeconomic status within ethnic groups (**Tables 7 and 8**) showed that Māori and Pacific children were more likely to live in socioeconomically deprived households than Asian and European/Other children. When Māori or Pacific ethnicity was defined using total response, the frequency of socioeconomic deprivation was lower than when self-prioritisation was used. When aggregated single-combined ethnicity was used, a greater proportion of Māori only, Pacific only, and Māori + Pacific (+/- other) children lived in socioeconomically deprived households than did Māori + non-Pacific or Pacific + non-Māori children, while the European/Other, Asian, and European/Other + Asian groups had the lowest proportions living in socioeconomically deprived households.

When the effect of socioeconomic deprivation on hospitalisation with an ID was examined within ethnic groups (**Tables 9 and 10**), there was a general trend towards an association between increased deprivation and increased rates of hospitalisation. Ethnic subgroup size was important as the relationship was more likely to reach statistical significance when larger, total response ethnic groups were used, and when the NZiDep was used in a binary form.

4.4 DISCUSSION

This study has demonstrated several methods of ascribing child ethnicity and socioeconomic status. Regardless of methodology, Māori and Pacific children, and children in the most socioeconomically deprived households, had a higher risk of hospitalisation for an ID. However, the magnitude of these effects varied between methods. The *Growing Up in New Zealand* cohort is large and includes representative proportions of Māori, Pacific, and socioeconomically deprived families (38, 39). In studies with lower statistical power, due to a smaller sample size or underrepresentation of disadvantaged population subgroups, the differences between methodologies are likely to be more important. There are also philosophical differences between methodologies which might make one method more appropriate than another in certain settings.

Ethnicity can be an area of significant individual and societal sensitivity, so the use of ethnicity data in research must be managed respectfully. Ethnicity is a self-determined construct deeply enmeshed with related aspects of identity including genetic or geographic ancestry, race, nationality, physical features, shared history, language or religion, and how society identifies the individual (149). The borders of ethnic categories are indistinct, and subject to local political considerations making international comparisons difficult. While the relationship between ethnicity and ancestry leads to a small degree of genetic variation between ethnic groups (152), this is minor compared to within-group variation, meaning ethnicity functions more as a marker of risk due to social factors than as a risk factor in itself (28, 153). That said, there are genetic conditions, such as sickle cell anaemia and other haemoglobinopathies thought to have a protective affect against malaria, for which the alleles associated with disease are more frequent in certain ethnic groups (122). Despite these complexities ethnicity remains an important variable in epidemiological studies which seek to document disparities in health outcomes and to guide health resource allocation (153, 154). However, many research articles compare outcomes by ethnic group without defining how ethnicity was determined. From a participant perspective, an ideal measure of ethnicity should be self-identified and capable of recording multiple ethnicities and the relative or equal importance of each. From a research perspective, the measure should remain simple to analyse and maintain subgroup size and statistical power.

External prioritisation to a single ethnicity, generally in the order Māori, Pacific, Asian, other non-European, then European, has fallen out of favour in NZ as it does not respect self-identification and fails to account for mixed ethnicities (150). In addition, external prioritisation maximises the size of the higher priority groups by including individuals who may share relatively little of the ethnic identity and social disadvantage common to that group. Therefore, it may underestimate the burden of excess morbidity experienced by individuals who would prioritise themselves to that ethnic group.

The methods demonstrated in this study were all self-identified but differed in the way they treated multiple ethnicities, with consequences for analysis and interpretation. Self-prioritisation did not allow multiple ethnicities and yielded a single non-overlapping ethnic group per participant. As individuals were assigned to the group their caregiver felt they identified with most, dilution of social disadvantage was reduced – this likely explains the slightly (though non-significantly) greater risk estimates seen when compared with total response. However, 11% of the cohort as a whole and 25% of total response Māori children were unable to be prioritised; caregivers either chose two ethnicities or declined to answer. Excluding these individuals had only a small effect on risk estimates but should not be seen as an appropriate response to this problem. Ethnic diversity within the Māori cohort, a parental preference for the transference of Māori ethnicity, and the concept of the indivisibility of whakapapa (genealogy or descent, meaning that a person of Māori descent is regarded as Māori regardless of the proportion of their Māori ancestry), likely explain why caregivers of Māori children were particularly disinclined to prioritise a single ethnicity (155-157).

Total response ethnicity allowed caregivers to identify multiple ethnicities simultaneously, but this overlap complicated analyses as no single comparator group was available. Philosophically, this lack of a comparator group has the advantage of avoiding the ethnocentric assumption that the comparator group has the desired level of the outcome (158). This benefit is lost if a residual non-overlapping group ('European/Other only' in this study) is used as a fixed comparator. Dilution of social disadvantage can be a problem where overlaps are large and can be further compounded by inclusion of other disadvantaged groups in the pooled comparator.

Single-combined ethnicity also allowed multiple ethnicities but without overlap between groups. Multiple combination groups were identified, some of which had few participants with consequent loss of power and difficulty presenting results coherently. Use of finer measures of ethnicity than the broad groups used in this study would exacerbate this effect further. Aggregating the smaller combination groups overcame this issue at the expense of loss of detail. A particular strength of the single-combined method was the ability to demonstrate the diversity of risk within the Māori and Pacific groups, as defined using self-prioritisation or total response, showing that these groups are not homogeneous.

Comparison of measures of socioeconomic status also identified several issues. This study compared household income with validated census-derived and survey-derived measures of socioeconomic deprivation which are commonly used in NZ. Household income proved problematic as a measure of financial resources. Previous research has documented that responses to questions regarding income are frequently incomplete, inaccurate, or declined. (159). Reasons for this can be informational, computational, or motivational (160). While both under- and over-reporting may occur (160), we found nonresponse to be most frequent amongst participants living in more deprived areas, creating a significant risk of bias if those with missing data were excluded. Participants living in more deprived areas were also more likely to provide post-tax income, compounding the risk of bias if only participants with pre-tax income were considered. As an additional limitation, the entire income amount may not necessarily be available as money may be used to pay interest on debt or may be diverted by charitable giving, particularly to religious institutions, or remittances to relatives overseas.

The NZDep2013 (47) and NZiDep (50, 51) performed similarly well in differentiating risk of hospitalisation for an ID across the socioeconomic gradient, despite having different underlying methodologies. The NZDep is updated after each national census (NZDep2013 being the update following the 2013 census) and made publically available, including in atlas form (161), so it has the advantage of a high level of completeness if the residential address is known. Similar census-derived indices of deprivation have been used in the United Kingdom (162), and in limited areas in the United States of America (163), and can be used to determine health resource allocation as well as research (164). There are a number of potential pitfalls

with using the NZDep. Firstly, the census questions used to derive the NZDep cover a range of social determinants of health. If similar variables, such as household crowding, are included with the NZDep in multivariable analyses, this creates a risk of multicollinearity. Secondly, deprivation is not homogeneous within NZDep deciles, therefore making assumptions about individuals within a given decile is a form of ecological fallacy. Comparison of NZiDep scores within NZDep2013 deciles showed that while high NZiDep scores were rare in the least deprived deciles, NZiDep scores of 1 or 2 were still common in the most deprived deciles, consistent with previous research in NZ (165).

The NZiDep required an additional eight questionnaire items but proved acceptable to participants with only 0.5% declining to answer one or more. While these questions covered employment and benefits, they didn't cover other social determinants of health such as crowding, meaning that these variables could also have been included in multivariable analyses. As individualised data was used, albeit for the caregiver rather than the child, the NZiDep largely avoided the ecological fallacy concerns affecting the NZDep. The proportion of the cohort with NZiDep scores of 3, 4, or 5 was small, leading to reduced statistical power. Creating a binary variable by comparing those scoring 3, 4, or 5 with those scoring 1 or 2 preserved the size of the more deprived subgroup and appeared to work well. This approach would require further validation before widespread use. The responses to specific NZiDep questions may also be of interest in their own right, and may highlight areas of hardship, such as food poverty, for policy intervention.

This study had some limitations. The use of broad ethnic groups was artificial. Only the Māori group represented an ethnicity many people would identify with. This approach obscured within-group mixed ethnicities, such as Tongan and Samoan, or Chinese and Korean. However, it is similar to Statistics New Zealand's use of 'level 1' ethnicity, and to the use of ethnicity in much international health research, and maintains statistical power. This study used ethnicity data obtained from the primary caregiver, most commonly the mother, and not their partner. Parents may have differed in their interpretation or weighting of their child's ethnicity (156). The intergenerational transmission of ethnicity is not straightforward, especially in inter-ethnic parental relationships or where one or both parents identify as mixed ethnicity themselves (155). The frequent use of the 'New Zealander' response was problematic. We included these children in the European/Other category but in reality the

group is heterogeneous. Similar issues have been faced in interpreting national census results (166). The NZiDep questions were not all taken verbatim from the validated questionnaire, so items describing employment status and receipt of benefits had to be recoded from alternative survey questions which closely approximated the NZiDep items. A high proportion (17.3%) of primary caregivers were not working due to childcare or family commitments. This scored a 'no' on the unemployment item and may have led to an underestimate of deprivation in some of these families. Neither of the socioeconomic deprivation indices directly described material deprivation at the level of the individual child. GUINZ has collected numerous additional variables describing social determinants of health including household crowding, housing quality, tobacco smoke exposure, healthcare access, exposure to racism, and others, all of which were intentionally excluded from this demonstration. GUINZ is a longitudinal study incorporating data from multiple data collection waves, however the current study used only cross-sectional data at 4½ years of child age. Further research is required to investigate longitudinal changes in child ethnic identity and socioeconomic mobility.

In summary, this study has demonstrated multiple methods of ascribing ethnicity and socioeconomic deprivation in a large and diverse child cohort. Self-prioritised, total response, and single combined ethnicity were all usable. Self-prioritisation was simplest to analyse, but 10% of participants could not be prioritised to a single ethnic group. Total response was complicated by overlap between groups and, in an unmodified form, did not allow a single baseline for comparison. Single-combined created a number of small ethnic groups with loss of statistical power, but aggregation overcame this. Single-combined ethnicity revealed diversity of risk within the broader Māori and Pacific groups and for this reason, and with mixed ethnicity becoming increasingly common, the single-combined method should be preferred where sample size and data structure allow it. Household income was affected by non-random missing data and the inability to combine pre-tax and post-tax income, both factors contributing to a risk of bias. Both NZDep2013 and the NZiDep were effective in differentiating risk between high and low levels of deprivation. The NZDep2013 requires caution with regards to the ecological fallacy and is most appropriate to studies which do not include social determinants of health which overlap with the census items used to derive the index. The NZiDep avoids these issues but requires a large sample size as a relatively small proportion of people are identified as having high deprivation scores. The questions from which the NZiDep is derived may be of interest in their own right.

4.5 TABLES

Table 1: Standard NZiDep questions and GUINZ questionnaire items used to derive NZiDep.

NZiDep 2014 question	GUINZ question	Responses		
		Yes (%)	No (%)	Missing (%)
1 – In the last 12 months have you personally been forced to buy cheaper food so that you could pay for other things you needed?	Unchanged	1994 (35.5)	3598 (64.2)	10 (0.2)
2 – In the last 12 months, have you been out of paid work at any time for more than one month?	Recoding from responses to multiple questions. See footnote.	555 (9.9)	5036 (89.9)	11 (0.2)
3 – In the 12 months ending today did you yourself receive payments from any of these three benefits: Jobseeker Support, Sole Parent Support or Supported Living Payment?	Which of the following are current sources of income for your household? Recoded from affirmative responses for: Jobseeker Support; Sole Parent Support; Supported Living Payment.	611 (10.9)	4984 (89.0)	<10 (0.1)
4 – In the last 12 months have you personally put up with feeling cold to save heating costs?	Unchanged	787 (14.0)	4809 (85.8)	<10 (0.1)
5 – In the last 12 months have you personally made use of special food grants or food banks because you did not have enough money for food?	Unchanged	506 (9.0)	5092 (90.9)	<10 (0.1)
6 – In the last 12 months have you personally continued wearing shoes with holes because you could not afford replacements?	Unchanged	541 (9.7)	5057 (90.3)	<10 (0.1)
7 – In the last 12 months have you personally gone without fresh fruit and vegetables, often, so that you could pay for other things you needed?	Unchanged	574 (10.2)	5022 (89.6)	<10 (0.1)
8 – In the last 12 months have you personally received help in the form of clothes or money from a community organisation (like the Salvation Army)?	Unchanged	256 (4.6)	5341 (95.3)	<10 (0.1)

Table 1 Footnote: The responses from multiple questions asked about primary caregiver employment status were recoded to derive a response to Question 2. These included: (1) Which of the following best describes your current situation in regard to paid work?; (2) How long have you been, or how long were you, seeking work?; and, (3) What is the MAIN reason you are not currently in paid work?

Table 2: Frequency of self-prioritised ethnic groups within total response ethnic groups for 5602 cohort children.

Self-prioritised ethnicity	**Total response ethnicity**			
	European/Other	**Māori**	**Pacific**	**Asian**
European/Other	3265 (76.1)	426 (30.9)	123 (11.0)	94 (11.4)
Māori	601 (14.0)	858 (62.2)	221 (19.8)	35 (4.3)
Pacific	239 (5.6)	92 (6.7)	767 (68.7)	39 (4.7)
Asian	187 (4.4)	<10 (<1.0)	<10 (<1.0)	655 (79.6)
Total	4292 (100.0)	1379 (100.0)	1117 (100.0)	823 (100.0)

Table 3: The effect of different methodologies of ascribing child ethnicity on relative risk for hospitalisation of an infectious disease (ID) in the first five years of life.

	n. (%)	ID hospitalisation		Unadjusted		Multivariable, [a]		Multivariable, corrected [a]	
		Yes	No	RR (95% CI)	P-value	RR (95% CI)	P-value	aRR (95% CI)	P-value
Self-prioritised ethnicity									
European/Other	3266 (58.3)	664 (20.3)	2602 (79.7)	Reference		Reference		Reference	
Māori	858 (15.3)	288 (33.6)	570 (66.4)	1.65 (1.47 – 1.85)	<0.0001	1.65 (1.47 – 1.85)	<0.0001	1.48 (1.30 – 1.67)	<0.0001
Pacific	777 (13.9)	332 (42.7)	445 (57.3)	2.10 (1.89 – 2.34)	<0.0001	2.10 (1.89 – 2.33)	<0.0001	1.79 (1.58 – 2.03)	<0.0001
Asian	701 (12.5)	169 (24.1)	532 (75.9)	1.19 (1.02 – 1.37)	0.03	1.19 (1.02 – 1.37)	0.03	1.14 (0.97 – 1.31)	0.10
Self-prioritised ethnicity, excl. dual/non-responses									
European/Other	3177 (63.7)	645 (20.3)	2532 (79.7)	Reference		Reference		Reference	
Māori	538 (10.8)	180 (33.5)	358 (66.5)	1.65 (1.44 – 1.89)	<0.0001	1.65 (1.43 – 1.89)	<0.0001	1.46 (1.25 – 1.68)	<0.0001
Pacific	655 (13.1)	288 (44.0)	367 (56.0)	2.17 (1.94 – 2.42)	<0.0001	2.17 (1.94 – 2.42)	<0.0001	1.81 (1.59 – 2.07)	<0.0001
Asian	621 (12.4)	152 (24.5)	469 (75.5)	1.21 (1.03 – 1.41)	0.02	1.21 (1.03 – 1.40)	0.02	1.15 (0.98 – 1.34)	0.08
Total response ethnicity									
European/Other	4292 (76.6)	978 (22.8)	3314 (77.2)	0.63 (0.57 – 0.69)	<0.0001	0.72 (0.64 – 0.81)	<0.0001	0.78 (0.69 – 0.88)	<0.0001
Māori	1379 (24.6)	424 (30.8)	955 (69.3)	1.26 (1.15 – 1.39)	<0.0001	1.20 (1.09 – 1.31)	0.0002	1.14 (1.04 – 1.26)	0.007
Pacific	1117 (19.9)	444 (39.8)	673 (60.3)	1.77 (1.61 – 1.93)	<0.0001	1.48 (1.32 – 1.65)	<0.0001	1.36 (1.21 – 1.52)	<0.0001
Asian	823 (14.7)	206 (25.0)	617 (75.0)	0.96 (0.84 – 1.09)	0.52	0.91 (0.79 – 1.05)	0.23	0.93 (0.80 – 1.07)	0.34
Total response ethnicity, fixed comparator group									
European/Other **ONLY**	2738 (48.9)	549 (20.1)	2189 (79.9)	Reference		Reference		Reference	
Māori	1379 (24.6)	424 (30.8)	955 (69.3)	1.53 (1.38 – 1.71)	<0.0001	1.19 (1.08 – 1.31)	0.0003	1.13 (1.02 – 1.24)	0.02
Pacific	1117 (19.9)	444 (39.8)	673 (60.3)	1.98 (1.79 – 2.20)	<0.0001	1.74 (1.59 – 1.91)	<0.0001	1.50 (1.35 – 1.66)	<0.0001
Asian	823 (14.7)	206 (25.0)	617 (75.0)	1.25 (1.09 – 1.44)	0.002	1.08 (0.95 – 1.22)	0.24	1.05 (0.92 – 1.19)	0.46

Table 3 continued	**n. (%)**	**ID hospitalisation**		**Unadjusted**		**Multivariable, [a]**		**Multivariable, corrected [a]**	
		Yes	**No**	**RR (95% CI)**	**P-value**	**RR (95% CI)**	**P-value**	**aRR (95% CI)**	**P-value**
Single-combined ethnicity									
European/Other only	2738 (48.9)	549 (20.1)	2189 (79.9)	Reference		Reference		Reference	
Māori only	157 (2.8)	64 (40.8)	93 (59.2)	2.03 (1.66 – 2.49)	<0.0001	2.03 (1.64 – 2.46)	<0.0001	1.76 (1.40 – 2.15)	<0.0001
Pacific only	476 (8.5)	216 (45.4)	260 (54.6)	2.26 (2.00 – 2.56)	<0.0001	2.26 (2.00 – 2.56)	<0.0001	1.89 (1.63 – 2.19)	<0.0001
Asian only	509 (9.1)	132 (25.9)	377 (74.1)	1.29 (1.10 – 1.53)	0.003	1.29 (1.09 – 1.52)	0.002	1.23 (1.04 – 1.45)	0.02
European + Māori	830 (14.8)	212 (25.5)	618 (74.5)	1.27 (1.11 – 1.46)	0.0007	1.27 (1.11 – 1.46)	0.0006	1.19 (1.03 – 1.36)	0.02
European + Pacific	247 (4.4)	74 (30.0)	173 (70.0)	1.49 (1.22 – 1.83)	0.0002	1.49 (1.21 – 1.82)	0.0001	1.37 (1.10 – 1.67)	0.003
European + Asian	211 (3.8)	43 (20.4)	168 (79.6)	1.02 (0.77 – 1.34)	0.91	1.02 (0.76 – 1.32)	0.91	0.99 (0.74 – 1.29)	0.95
Māori + Pacific	133 (2.4)	50 (37.6)	83 (62.4)	1.87 (1.49 – 2.36)	<0.0001	1.88 (1.46 – 2.33)	<0.0001	1.59 (1.23 – 2.00)	0.0002
Māori + Asian	<10 (<0.2)	<10 (42.9)	<10 (57.1)	2.14 (0.91 – 5.04)	0.15	2.14 (0.64 – 3.89)	0.08	1.95 (0.59 – 3.52)	0.13
Pacific + Asian	22 (0.4)	<10 (36.4)	14 (63.6)	1.81 (1.04 – 3.17)	0.06	1.81 (0.92 – 2.87)	0.04	1.57 (0.80 – 2.49)	0.11
European + Māori + Pacific	197 (3.5)	82 (41.6)	115 (58.4)	2.08 (1.73 – 2.49)	<0.0001	2.08 (1.72 – 2.47)	<0.0001	1.84 (1.51 – 2.21)	<0.0001
European + Māori + Asian	32 (0.6)	<10 (18.8)	26 (81.3)	0.94 (0.45 – 1.93)	0.85	0.94 (0.39 – 1.73)	0.86	0.88 (0.37 – 1.62)	0.72
European + Pacific + Asian	19 (0.3)	<10 (36.8)	12 (63.2)	1.84 (1.02 – 3.33)	0.07	1.84 (0.89 – 2.98)	0.04	1.64 (0.79 – 2.65)	0.10
Māori + Pacific + Asian	<10 (<0.2)	<10 (40.0)	<10 (60.0)	1.99 (0.68 – 5.85)	0.26	2.00 (0.40 – 4.02)	0.21	1.61 (0.32 – 3.28)	0.39
European + Māori + Pacific + Asian	18 (0.3)	<10 (27.8)	13 (72.2)	1.39 (0.66 – 2.93)	0.38	1.39 (0.55 – 2.53)	0.39	1.26 (0.50 – 2.30)	0.54
Single-combined ethnicity, aggregated combinations									
European/Other only	2738 (48.9)	549 (20.1)	2189 (80.0)	Reference		Reference		Reference	
Māori only	157 (2.8)	64 (40.8)	93 (59.2)	2.03 (1.66 – 2.49)	<0.0001	2.03 (1.64 – 2.46)	<0.0001	1.76 (1.40 – 2.15)	<0.0001
Pacific only	476 (8.5)	216 (45.4)	260 (54.6)	2.26 (2.00 – 2.56)	<0.0001	2.26 (2.00 – 2.56)	<0.0001	1.89 (1.63 – 2.19)	<0.0001
Asian only	509 (9.1)	132 (25.9)	377 (74.1)	1.29 (1.10 – 1.53)	0.003	1.29 (1.09 – 1.52)	0.002	1.23 (1.04 – 1.45)	0.02
Māori + non-Pacific	869 (15.5)	221 (25.4)	648 (74.6)	1.27 (1.11 – 1.45)	0.0007	1.27 (1.10 – 1.45)	0.0006	1.18 (1.03 – 1.36)	0.02
Pacific + non-Māori	288 (5.1)	89 (30.9)	199 (69.1)	1.54 (1.28 – 1.86)	<0.0001	1.54 (1.27 – 1.85)	<0.0001	1.40 (1.15 – 1.69)	0.0006
Māori + Pacific +/- others	353 (6.3)	139 (39.4)	214 (60.6)	1.96 (1.69 – 2.28)	<0.0001	1.96 (1.68 – 2.27)	<0.0001	1.71 (1.45 – 2.00)	<0.0001
European + Asian	211 (3.8)	43 (20.4)	168 (79.6)	1.02 (0.77 – 1.34)	0.91	1.02 (0.76 – 1.32)	0.91	0.99 (0.74 – 1.29)	0.95

Table 3 footnote: [a] The multivariable model was first constructed with only the multiple levels of the relevant ethnicity variable. The 'corrected' column represents the same model after correction for socioeconomic status using the NZDep2013.

Table 4: Comparison of the proportion of children from corresponding ethnic groups hospitalised for an infectious disease (ID) using different methodologies of ascribing child ethnicity

	Percentage (95% CI) hospitalised for an ID by methodology of ascribing ethnicity			Risk difference	P-value
Ethnic group method comparison	**Self-prioritised**	**Total response**	**Single-combined**		
Self-prioritised vs. total response					
SP European/Other vs. TR European/Other	20.3 (0.19 – 0.22)	22.8 (0.22 – 0.24)		-2.5 (-4.3 – -0.6)	0.01
SP Māori vs. TR Māori	33.6 (0.30 – 0.37)	30.8 (0.28 – 0.33)		2.8 (-1.2 – 6.8)	0.16
SP Pacific vs. TR Pacific	42.7 (0.39 – 0.46)	39.8 (0.37 – 0.43)		3.0 (-1.5 – 7.5)	0.19
SP Asian vs. TR Asian	24.1 (0.21 – 0.27)	25.0 (0.22 – 0.28)		-0.9 (-5.3 – 3.4)	0.68
Self-prioritised vs. single-combined					
SP European/Other vs. SC European/Other only	20.3 (0.19 – 0.22)		20.1 (0.19 – 0.22)	-0.3 (-2.3 – 1.8)	0.79
SP European/Other vs. SC European + Asian	20.3 (0.19 – 0.22)		20.4 (0.15 – 0.26)	0.1 (-5.6 – 5.7)	0.99
SP Māori vs. SC Māori only	33.6 (0.30 – 0.37)		40.8 (0.33 – 0.48)	7.2 (-1.1 – 15.5)	0.08
SP Māori vs. SC Māori + non-Pacific	33.6 (0.30 – 0.37)		25.4 (0.23 – 0.28)	-8.1 (-12.4 – -3.9)	0.0002
SP Māori vs. SC Māori + Pacific +/- others	33.6 (0.30 – 0.37)		39.4 (0.34 – 0.44)	5.8 (-0.2 – 11.8)	0.05
SP Pacific vs. SC Pacific only	42.7 (0.39 – 0.46)		45.4 (0.41 – 0.50)	2.7 (-3.0 – 8.3)	0.36
SP Pacific vs. SC Pacific + non-Māori	42.7 (0.39 – 0.46)		30.9 (0.26 – 0.36)	-11.8 (-18.2 – -5.5)	0.0005
SP Pacific vs. SC Māori + Pacific +/- others	42.7 (0.39 – 0.46)		39.4 (0.34 – 0.44)	-3.4 (-9.5 – 2.8)	0.29
SP Asian vs. SC Asian only	24.1 (0.21 – 0.27)		25.9 (0.22 – 0.30)	1.8 (-3.1 – 6.8)	0.47
SP Asian vs. SC European + Asian	24.1 (0.21 – 0.27)		20.4 (0.15 – 0.26)	-3.7 (-10 – 2.6)	0.26

Table 4 continued	**Percentage (95% CI) hospitalised for an ID by methodology of ascribing ethnicity**			**Risk difference**	**P-value**
Ethnic group method comparison	**Self-prioritised**	**Total response**	**Single-combined**		
Total response vs. single-combined					
TR European/Other vs. SC European/Other only		22.8 (0.22 – 0.24)	20.1 (0.19 – 0.22)	-2.7 (-4.7 – -0.8)	0.007
TR European/Other vs. SC European + Asian		22.8 (0.22 – 0.24)	20.4 (0.15 – 0.26)	-2.4 (-8.0 – 3.2)	0.41
TR Māori vs. SC Māori only		30.8 (0.28 – 0.33)	40.8 (0.33 – 0.48)	10.0 (2.0 – 18.1)	0.01
TR Māori vs. SC Māori + non-Pacific		30.8 (0.28 – 0.33)	25.4 (0.23 – 0.28)	-5.3 (-9.1 – -1.5)	0.007
TR Māori vs. SC Māori + Pacific +/- others		30.8 (0.28 – 0.33)	39.4 (0.34 – 0.44)	8.6 (3.0 – 14.3)	0.002
TR Pacific vs. SC Pacific only		39.8 (0.37 – 0.43)	45.4 (0.41 – 0.50)	5.6 (0.3 – 10.9)	0.04
TR Pacific vs. SC Pacific + non-Māori		39.8 (0.37 – 0.43)	30.9 (0.26 – 0.36)	-8.9 (-14.9 – -2.8)	0.006
TR Pacific vs. SC Māori + Pacific +/- others		39.8 (0.37 – 0.43)	39.4 (0.34 – 0.44)	-0.4 (-6.2 – 5.5)	0.9
TR Asian vs. SC Asian only		25.0 (0.22 – 0.28)	25.9 (0.22 – 0.30)	0.9 (-3.9 – 5.7)	0.71
TR Asian vs. SC European + Asian		25.0 (0.22 – 0.28)	20.4 (0.15 – 0.26)	-4.7 (-10.8 – 1.5)	0.16

Table 4 footnote: SC = single-combined ethnicity, SP = self-prioritised ethnicity, TR = total response ethnicity

Table 5: The effect of different methodologies of ascribing socioeconomic status on relative risk of hospitalisation for an infectious disease (ID) in the first five years of life.

				Unadjusted		Multivariable [a]		Multivariable, corrected [a]	
	n (%)	**ID hospitalisation**		**RR (95% CI)**	**P–value**	**RR (95% CI)**	**P–value**	**aRR (95% CI)**	**P–value**
		Yes	**No**						
NZDep2013 deciles									
1 – 2	1191 (21.3)	231 (19.4)	960 (80.6)	Reference		Reference		Reference	
3 – 4	1087 (19.4)	221 (20.3)	866 (79.7)	1.05 (0.89 – 1.24)	0.58	1.05 (0.89 – 1.24)	0.58	1.01 (0.86 – 1.19)	0.90
5 – 6	999 (17.8)	241 (24.1)	758 (75.9)	1.24 (1.06 – 1.46)	0.007	1.24 (1.06 – 1.46)	0.007	1.16 (0.99 – 1.36)	0.07
7 – 8	952 (17.0)	261 (27.4)	691 (72.6)	1.41 (1.21 – 1.65)	<0.0001	1.41 (1.21 – 1.65)	<0.0001	1.21 (1.03 – 1.42)	0.02
9 – 10	1373 (24.5)	499 (36.3)	874 (63.7)	1.87 (1.64 – 2.15)	<0.0001	1.87 (1.64 – 2.15)	<0.0001	1.38 (1.18 – 1.60)	<0.0001
NZiDep score									
1	3071 (55.1)	668 (21.8)	2403 (78.3)	Reference		Reference		Reference	
2	1161 (20.8)	295 (25.4)	866 (74.6)	1.17 (1.04 – 1.32)	0.01	1.17 (1.04 – 1.31)	0.01	1.08 (0.95 – 1.21)	0.22
3	531 (9.5)	171 (32.2)	360 (67.8)	1.48 (1.29 – 1.70)	<0.0001	1.48 (1.28 – 1.70)	<0.0001	1.29 (1.12 – 1.48)	0.0004
4	500 (9.0)	186 (37.2)	314 (62.8)	1.71 (1.50 – 1.95)	<0.0001	1.71 (1.49 – 1.95)	<0.0001	1.37 (1.19 – 1.57)	<0.0001
5	309 (5.6)	119 (38.5)	190 (61.5)	1.77 (1.51 – 2.07)	<0.0001	1.77 (1.51 – 2.06)	<0.0001	1.30 (1.10 – 1.52)	0.002
NZiDep score, binary									
1 – 2	4232 (76.0)	963 (22.8)	3269 (77.2)	Reference		Reference		Reference	
3 – 5	1340 (24.1)	476 (35.5)	864 (64.5)	1.56 (1.43 – 1.71)	<0.0001	1.56 (1.42 – 1.71)	<0.0001	1.29 (1.17 – 1.42)	<0.0001

Table 5 footnote: [a] The multivariable model was first constructed with only the multiple levels of the relevant socioeconomic variable. The 'corrected' column represents the same model after correction for ethnicity using the self-prioritised ethnic group method.

Table 6: Frequency of NZiDep score within NZDep2013 deciles for the primary caregivers of 5602 cohort children.

NZiDep Score	**NZDep2013 Deciles**				
	1 to 2	**3 to 4**	**5 to 6**	**7 to 8**	**9 to 10**
1	854 (71.95)	739 (68.11)	601 (60.46)	465 (49.26)	412 (30.25)
2	221 (18.62)	220 (20.28)	206 (20.72)	213 (22.56)	301 (22.10)
3	70 (5.90)	65 (5.99)	99 (9.96)	109 (11.55)	188 (13.80)
4	33 (2.78)	46 (4.24)	62 (6.24)	93 (9.85)	266 (19.53)
5	<10 (<1.0)	15 (1.38)	26 (2.62)	64 (6.78)	195 (14.32)
1 to 2	1075 (90.56)	959 (88.39)	807 (81.19)	678 (71.82)	713 (52.35)
3 to 5	112 (9.44)	126 (11.61)	187 (18.81)	266 (28.18)	649 (47.65)
Total	1187 (100.0)	1085 (100.0)	994 (100.0)	944 (100.0)	1362 (100.0)

Table 7: Socioeconomic status (NZDep2013 and NZiDep) within self-prioritised and total response ethnic groups.

	Self-prioritised ethnicity, n (%)				Total response ethnicity, n (%)			
	Euro/Other	**Māori**	**Pacific**	**Asian**	**Euro/Other**	**Māori**	**Pacific**	**Asian**
NZDep2013 deciles								
1 – 2	994 (30.4)	71 (8.3)	21 (2.7)	105 (15.0)	1110 (25.9)	168 (12.2)	45 (4.0)	129 (15.7)
3 – 4	782 (23.9)	90 (10.5)	49 (6.3)	166 (23.7)	931 (21.7)	172 (12.5)	96 (8.6)	182 (22.1)
5 – 6	674 (20.6)	125 (14.6)	65 (8.4)	135 (19.3)	844 (19.7)	224 (16.2)	113 (10.1)	157 (19.1)
7 – 8	475 (14.5)	187 (21.8)	135 (17.4)	155 (22.1)	700 (16.3)	283 (20.5)	201 (18.0)	176 (21.4)
9 – 10	341 (10.4)	385 (44.9)	507 (65.3)	140 (20.0)	707 (16.5)	532 (38.6)	662 (59.3)	179 (21.8)
NZiDep score								
1	2074 (63.7)	306 (36.0)	216 (27.9)	475 (68.7)	2515 (58.8)	540 (39.4)	353 (31.8)	524 (64.5)
2	650 (20.0)	199 (23.4)	176 (22.8)	136 (19.7)	897 (21.0)	317 (23.2)	248 (22.3)	170 (20.9)
3	274 (8.4)	118 (13.9)	99 (12.8)	40 (5.8)	397 (9.3)	191 (14.0)	149 (13.4)	54 (6.6)
4	184 (5.7)	137 (16.1)	150 (19.4)	29 (4.2)	314 (7.3)	198 (14.5)	194 (17.5)	45 (5.5)
5	76 (2.3)	90 (10.6)	132 (17.1)	11 (1.6)	157 (3.7)	123 (9.0)	166 (15.0)	20 (2.5)
1 – 2	2724 (83.6)	505 (59.4)	392 (50.7)	611 (88.4)	3412 (79.7)	857 (62.6)	601 (54.1)	694 (85.4)
3 – 5	534 (16.4)	345 (40.6)	381 (49.3)	80 (11.6)	868 (20.3)	512 (37.4)	509 (45.9)	119 (14.6)

Table 8: Socioeconomic status (NZDep2013 and NZiDep) within aggregated single-combined ethnic groups.

	Single-combined ethnic group, n (%)							
	Euro/Other only	**Māori only**	**Pacific only**	**Asian only**	**Māori + non-Pacific**	**Pacific + non-Māori**	**Māori + Pacific**	**Euro/Other + Asian**
NZDep2013 deciles								
1 – 2	873 (31.9)	<10 (5.1)	<10 (0.6)	67 (13.2)	145 (16.7)	27 (9.4)	15 (4.3)	52 (24.6)
3 – 4	679 (24.8)	10 (6.4)	15 (3.2)	120 (23.6)	134 (15.4)	53 (18.4)	28 (7.9)	48 (22.8)
5 – 6	562 (20.5)	10 (6.4)	28 (5.9)	107 (21.0)	173 (19.9)	44 (15.3)	41 (11.6)	34 (16.1)
7 – 8	390 (14.2)	43 (27.4)	72 (15.1)	108 (21.2)	163 (18.8)	52 (18.1)	77 (21.8)	47 (22.3)
9 – 10	234 (8.6)	86 (54.8)	358 (75.2)	107 (21.0)	254 (29.2)	112 (38.9)	192 (54.4)	30 (14.2)
NZiDep score								
1	1804 (66.0)	45 (29.0)	115 (24.3)	351 (70.3)	381 (44.1)	124 (43.2)	114 (32.6)	136 (64.5)
2	531 (19.4)	35 (22.6)	101 (21.4)	96 (19.2)	207 (24.0)	72 (25.1)	75 (21.4)	44 (20.9)
3	204 (7.5)	21 (13.6)	59 (12.5)	27 (5.4)	115 (13.3)	35 (12.2)	55 (15.7)	15 (7.1)
4	142 (5.2)	29 (18.7)	104 (22.0)	17 (3.4)	106 (12.3)	27 (9.4)	63 (18.0)	12 (5.7)
5	51 (1.9)	25 (16.1)	94 (19.9)	<10 (1.6)	55 (6.4)	29 (10.1)	43 (12.3)	<10 (1.9)
1 – 2	2335 (85.5)	80 (51.6)	216 (45.7)	447 (89.6)	588 (68.1)	196 (68.3)	189 (54.0)	180 (85.3)
3 – 5	397 (14.5)	75 (48.4)	257 (54.3)	52 (10.4)	276 (31.9)	91 (31.7)	161 (46.0)	31 (14.7)

Table 9: Percentage of children hospitalised for an ID within self-prioritised and total response ethnic groups, by measure of socioeconomic status (NZDep2013 and NZiDep).

	Self-prioritised ethnic group								Total response ethnic group							
	Euro/Other		Māori		Pacific		Asian		Euro/Other		Māori		Pacific		Asian	
	%	P	%	P	%	P	%	P	%	P	%	P	%	P	%	P
NZDep2013																
1 – 2	18.7		23.9		38.1		19.1		19.4		23.2		40.0		16.3	
3 – 4	19.1		25.6		40.8		17.5		20.0		23.3		29.2		17.6	
5 – 6	20.5	0.07	31.2	0.07	35.4	0.11	30.4	0.03	22.3	<0.0001	26.8	0.001	33.6	0.004	30.6	0.0005
7 – 8	21.9		34.2		34.8		29.7		24.3		32.9		33.3		33.5	
9 – 10	25.5		37.7		46.2		23.6		31.0		36.1		44.3		25.7	
NZiDep score																
1	18.8		28.1		36.6		24.0		20.2		26.3		32.6		23.1	
2	18.8		35.2		40.3		23.5		22.9		28.1		39.5		24.7	
3	27.0	0.0001	37.3	0.09	42.4	0.04	27.5	0.77	28.7	<0.0001	36.7	0.004	40.9	0.004	37.0	0.24
4	29.4		34.3		52.7		20.7		30.9		34.9		49.0		26.7	
5	27.6		42.2		44.7		9.1		31.2		39.8		43.4		30.0	
1 – 2	18.8	<0.0001	30.9	0.05	38.3	0.01	23.9	0.78	20.9	<0.0001	27.0	0.0001	35.4	0.002	23.5	0.05
3 – 5	27.9		37.4		47.2		22.5		30.0		36.7		44.8		31.9	

Table 10: Percentage of children hospitalised for an ID within aggregated single-combined ethnic groups, by measure of socioeconomic status (NZDep2013 and NZiDep).

	Aggregated single-combined ethnic group															
	Euro/Other only		Māori only		Pacific only		Asian only		Māori + non-Pacific		Pacific + non-Māori		Māori + Pacific		Euro/Other + Asian	
	%	P	%	P	%	P	%	P	%	P	%	P	%	P	%	P
NZDep2013																
1 – 2	18.9		25.0		33.3		17.9		18.6		25.9		66.7		13.5	
3 – 4	19.0		70.0		46.7		15.8		20.9		30.2		17.9		20.8	
5 – 6	20.5	0.02	30.0	0.17	35.7	0.74	33.6	0.001	23.7	0.01	27.3	0.70	39.0	0.005	23.5	0.70
7 – 8	19.0		32.6		41.7		36.1		34.4		26.9		29.9		23.4	
9 – 10	28.2		44.2		46.9		24.3		27.2		35.7		44.3		23.3	
NZiDep score																
1	18.7		37.8		37.4		25.4		22.6		26.6		34.2		16.9	
2	19.8		34.3		45.5		22.9		22.2		29.2		41.3		27.3	
3	23.0	0.01	42.9	0.51	42.4	0.17	40.7	0.36	33.9	0.04	40.0	0.45	40.0	0.62	26.7	0.29
4	30.3		37.9		53.9		23.5		27.4		37.0		46.0		33.3	
5	25.5		56.0		47.9		12.5		34.6		37.9		37.2		0.0	
1 – 2	19.0	0.001	36.3	0.25	41.2	0.09	24.8	0.35	22.5	0.004	27.6	0.06	37.0	0.38	19.4	0.42
3 – 5	25.9		45.3		49.0		30.8		31.5		38.5		41.6		25.8	

CHAPTER 5: ANTIBIOTIC CONSUMPTION BY NEW ZEALAND CHILDREN: EXPOSURE NEAR-UNIVERSAL BY THE AGE OF FIVE YEARS

In Chapter 4, the self-prioritised method of ascribing child ethnicity was found to be a suitable for use in subsequent projects, and both the NZDep2013 and NZiDep were suitable for ascribing socioeconomic deprivation. This chapter uses self-prioritised ethnicity and the NZDep2013 to examine ethnic and socioeconomic differences in the dispensing of antibiotics from community pharmacies for children in the Growing Up in New Zealand cohort.

Community antibiotic use was found to be high amongst New Zealand children when compared with other developed countries. This finding was consistent with previous evidence from NZ and likely reflected excessive prescribing for self-limiting childhood illnesses. When antibiotics are given for a self-limiting illness, these children are exposed to a significant risk of antibiotic-related harm for little benefit. Such harms can include allergic reactions, other direct adverse effects such as gastrointestinal disturbance, the acquisition of antibiotic-resistant organisms, and perturbations of the host microbiome which may influence the risk of developing atopic or autoimmune disease and weight gain. On a societal level, heavy use of antibiotics encourages the spread of antibiotic-resistant clones of bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA).

These results could also be interpreted as indicating a very large burden of infectious disease managed in primary care. The proportion of cases of ID managed in primary care is much larger than that managed in hospital but is difficult to measure. While hospital discharge diagnoses are recorded in a national administrative database, this is not the case for primary care diagnoses in New Zealand. However, there are some important caveats to viewing dispensing data this way. Firstly, some prescriptions filled at community pharmacies will have been provided on hospital discharge. Secondly, many childhood infections are self-limiting and do not require antibiotic therapy, so the number of general practice attendances for infection is likely to be much higher than the number of antibiotic prescriptions filled. Thirdly, prescribing antibiotics for a self-limiting illness in which they are of no benefit is poor practice so the number of antibiotic prescriptions filled may reflect the quality of primary

care received. Fourthly, general practitioners may be more likely to provide a prescription to be filled immediately or if symptoms fail to resolve if they perceive the patient will have difficulty returning for reassessment – this could increase the frequency with which prescriptions are provided to patients in lower socioeconomic areas.

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Hobbs MR, Grant CC, Ritchie SR, Chelimo C, Morton SMB, Berry S, Thomas MG. Antibiotic consumption by New Zealand children: exposure is near universal by the age of 5 years. *The Journal of Antimicrobial Chemotherapy*. 2017;72(6):1832-40.

5.1 INTRODUCTION

Alongside improvements in public health and hygiene, antibiotics have played a major role in reducing infectious disease morbidity and mortality during the past 65 years. As a consequence, antibiotics are the medications most commonly prescribed for young children (53, 167, 168).

However, the relatively unrestrained use of antibiotics has resulted in increases in antibiotic resistance that threaten our ability to effectively treat infections (169, 170). As a result, many countries have introduced antimicrobial stewardship programmes which encourage appropriate antibiotic prescribing. High priorities for antimicrobial stewardship programmes include reducing the use of antibiotics for illnesses for which the probability of a bacterial aetiology is low, and reducing the inappropriate use of broad-spectrum antibiotics for bacterial infections (171, 172). The need for antimicrobial stewardship is highlighted by the substantial variability in antibiotic use between countries, between regions within countries, and between individual prescribers (173, 174). There is also a growing understanding that antibiotics, particularly if given very early in life, may have a range of undesirable effects, including increased weight gain (175, 176), or the development of immunologically-mediated disease (177, 178), thought to be related to disruption of the child's developing microbiome.

Previous research has shown that the overall level of antibiotic dispensing in the New Zealand (NZ) community is higher than in most European countries with the highest levels of dispensing in young children and the elderly (65). A study, conducted in a largely rural region of New Zealand, showed that the level of antibiotic dispensing for rural Māori (the indigenous people of NZ) children, was lower than the level for rural European children, raising concern that Māori children may have had restricted access to medical care (69).

In order to inform a national strategy to address the rising rate of antibiotic resistance in NZ, we aimed to describe community antibiotic dispensing in the first five years of life in a diverse cohort of NZ children, and to determine how antibiotic dispensing varied between population subgroups.

5.2 METHODS

5.2.1 Study design

This study was conducted within the *Growing Up in New Zealand* (GUINZ [www.growingup.co.nz]) longitudinal birth cohort study, using data obtained from parental interviews and from linkage to the Pharmaceutical Collection, a national administrative dataset comprising records of subsidised prescription medications dispensed from community pharmacies (52). GUINZ enrolled 6822 pregnant women with an estimated delivery date between 25th April 2009 and 25th March 2010. The 6853 cohort children were born to 6760 of these mothers. The ethnic and socioeconomic characteristics of the cohort were very similar to those of the total NZ birth cohort (38, 39).

In NZ, antibiotics for systemic use are only available with a prescription, and antibiotics are dispensed free of charge for children under the age of six years (179). Each of these fully subsidised dispensings from a community pharmacy is recorded in the Pharmaceutical Collection that is stored by the Ministry of Health (180).

5.2.2 Ethics

Ethical approval for the cohort study was obtained from the Ministry of Health Northern Y Regional Ethics Committee. Data from interviews, and from administrative health datasets, for each participating child, from birth to age 5 years, was obtained only for those children whose primary caregiver provided written informed consent.

5.2.3 Measures and Definitions

Explanatory variables were obtained from parental interviews and linked census-derived data. Variables of interest included child ethnicity, gender, household socioeconomic deprivation, and residence in an urban or rural area. Ethnicity was defined as the principal ethnic group nominated by the parent(s) at the interview completed when the cohort children were 4½ years old. For the purposes of analysis, ethnicity was grouped into the Statistics NZ level 1 ethnic

categorisation: Māori, Pacific, European, Asian, and 'Other' (166). As numbers in the 'Other' category were low (n=63), these children were combined with the European group for analysis. Household socioeconomic deprivation was measured using the NZDep2013 index, a small geographic area census-derived measure of household socioeconomic deprivation, assigned according to the address at which the child lived at the time of the 4½ year interview (47). The NZDep2013 index is reported in deciles, with decile 1 being the least deprived and decile 10 the most deprived 10% of NZ households. From the NZDep2013 index, three groups representing low (deciles 1 – 3), intermediate (deciles 4 – 7), and high (deciles 8 – 10) levels of socioeconomic deprivation were created. Rural residence was defined as residence in a rural area according to the Statistics New Zealand Classification of Urban Areas (49).

The Pharmaceutical Collection includes a record of all prescription medicines dispensed for which a community pharmacist has sought government subsidisation (180). The Pharmaceutical Collection does not include information on hospital inpatient dispensing, or medications dispensed directly by a medical practitioner in an emergency situation (180). Data were obtained for antibiotics that were coded under the Anatomical Therapeutic Chemical (ATC) system as J01: antibacterials for systemic use (181). Antibiotics were further identified by class (e.g. macrolides, cephalosporins), and in the case of penicillin antibiotics, by individual medication (e.g. amoxicillin, flucloxacillin). Topical antibacterial preparations, and topical or systemic antifungal, antiviral, or antiparasitic medications were excluded.

The primary outcome variable was the number of antibiotic courses dispensed per child before the age of five years. This measure was used in preference to DDD as DDDs are based on typical adult doses and are not appropriate for young children (182, 183). Where multiple antibiotic agents were dispensed on the same day, this was regarded as a single course. Antibiotic courses dispensed on separate days were regarded as separate courses, regardless of the degree of separation in time. Secondary outcomes included the proportion of children dispensed an antibiotic course by year of age, and the number of days of antibiotic dispensed per course. Days dispensed could only be calculated where adequate information to do so was provided (i.e. either if the number of days was recorded, or if a combination of the total amount dispensed, the amount per dose, and the dose frequency were recorded). Hospital discharge diagnostic coding records were reviewed to identify potential indications for

antibiotic prophylaxis use for children dispensed >40 antibiotic courses before the age of five, or one or more courses of ≥28 days.

5.2.4 Statistical analysis

Data were analysed using descriptive statistics, the Mann-Whitney-Wilcoxon test and multivariable negative binomial regression for numerical outcomes, and the chi-squared test for categorical outcomes. The Kolomgarov-Smirnov test was used to derive p-values for comparisons between cumulative distribution functions. Associations identified from regression analysis were reported as incidence rate ratios (IRR) and 95% CI, and were corrected for birth month. Graphs were used to show the frequency distribution of the number of antibiotic courses dispensed by the age of five years, the cumulative distribution function of first antibiotic dispensing, and the relationships between 1-month prevalence of antibiotic dispensing, child age and calendar month. P-values of <0.05 were considered statistically significant. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

5.3 RESULTS

The 4 ½ year interview was completed for 90% of the cohort (6156/6853). Consent to access administrative health data was provided by the primary caregiver for 5670/6156 (92%). Of these 5670 children, 89 were excluded from further analysis due to: non-residence in NZ during one or more of the face-to-face interviews completed when the cohort children were 9 months, 2 years or 4½ years old (83 children); evidence of a linkage mismatch (4 children); missing household and social data (1 child); and possible indication for long-term antibiotic prophylaxis (1 child).

Community pharmaceutical dispensing data from birth to age 5 years was available for 5581 (100%) children. The 5581 children were dispensed a total of 215,847 prescriptions of all medication types, of which 53,052/215,847 (25%) were for an antibiotic. The most frequently dispensed antibiotic class was the penicillins (38,724/53,052, 73%), with 28,813/38,724, (74%) of penicillin dispensings being for amoxicillin. Trimethoprim-sulphamethoxazole

(5587/53,052, 11%), cephalosporins (5002/53,052, 9%), and macrolides (3722/53,052, 7%) were the next most frequently dispensed antibiotics, with other classes comprising only 15/53,052 (0.03%) (**Table 11**). The number of days of antibiotics dispensed per course was able to be determined for 42,752/53,052 (81%) of the antibiotic courses. For these courses, the median number of days per antibiotic course was 7 (IQR 7 – 8) days.

Overall, 5408/5581 (97%) children had been dispensed one or more antibiotic courses by the age of five years, with 86%, 92%, and 95% having been dispensed one or more antibiotic courses by the ages of two, three, and four years respectively. 3457/5581 (62%) of the cohort children had been dispensed antibiotics during the first year of life; and 77%, 73%, 70%, and 66% had been dispensed antibiotics during the second, third, fourth, and fifth years respectively, giving a mean annual prevalence of 70%. The proportion of children who had been dispensed one or more antibiotic courses was higher for Māori and for Pacific children than for European children during each year of life (P<0.001) (**Table 12**). Māori and Pacific children had been dispensed their first antibiotic courses at younger ages than children of other ethnicities (**Figure 1**). The age at dispensing of their first antibiotic course did not differ between children of European, Asian and Other ethnicity. The median time to the first antibiotic course was 6.9 months for Pacific children, 8.1 months for Māori children, and 10.8 months for all other children (P<0.001).

The proportion of children who had been dispensed an antibiotic course in each month of life increased steadily during the first year of life, from 123/5581 (2%) in the first month of life, to a peak of 1145/5581 (21%) in the 12th month of life (**Figure 2**). Thereafter, there was an overall gradual decrease in the monthly prevalence of antibiotic dispensing (P<0.001 for difference in trend). Superimposed on this age-related pattern, was marked seasonal variation. When analysis was restricted to months in which data from the complete cohort were available for analysis (from completion of enrolment on 1 April 2010 until the beginning of exclusion at age 5 on 1 April 2014), 35% of antibiotic courses were dispensed in the winter quarter (June to August) compared with 17% in the summer quarter (December to February) (P<0.001) (**Figure 3**).

Each child was dispensed a median of 8 antibiotic courses (IQR 4 – 13) by the age of 5 years (**Figure 4**). In unadjusted analyses, boys received a higher median number of antibiotic courses before the age of five years than girls (boys 8 (IQR 4 – 14), girls 7 (IQR 4 – 12), P<0.001) and children living in rural areas received fewer antibiotic courses than children living in urban areas (**Table 13**). Children of Māori, Pacific, Asian and 'Other' ethnicities all received a significantly higher median number of antibiotic courses in comparison with children of European ethnicity. Children living in areas of high, socioeconomic deprivation received more antibiotic courses than did children living in areas of low socioeconomic deprivation.

The incidence of antibiotic dispensing was 1.9 antibiotic courses dispensed per child per year (standard deviation 1.5) over the first 5 years of life. Multivariable negative binomial regression was used to estimate incidence rate ratios, controlling for gender, ethnicity, socioeconomic deprivation, rurality, and birth month. The incidence rate of antibiotic dispensing was higher in Māori, Pacific, and Asian children compared with European children, and was higher for children living in households of high compared with low socioeconomic deprivation (**Table 14**). The incidence rate was lower in children living in rural compared with urban areas.

When the multivariable analysis was stratified by ethnicity (**Table 15**), rural residence was associated with a reduced incidence of antibiotic dispensing for European children (IRR 0.87, 95% CI 0.80 – 0.95, p=0.001), but this trend was not significant for Māori children (IRR 0.88, 95% CI 0.74 – 1.04, p=0.13). A high level of socioeconomic deprivation was associated with an increased incidence of antibiotic dispensing for Māori (IRR 1.29, 95% CI 1.08 – 1.53, p=0.004) and Pacific (IRR 1.26, 95% CI 1.03 – 1.53, p=0.02) children, but socioeconomic deprivation was not associated with the incidence of antibiotic dispensing for European/Other or Asian children. For the analyses within the Pacific, Asian or Other ethnic groups, the association between rural residence and antibiotic dispensing rates could not be assessed because of the small numbers of these children residing in rural regions. The multivariable analysis stratified by socioeconomic deprivation is presented in **Table 16**.

5.4 DISCUSSION

In this study of antibiotic dispensing in a large, representative cohort of NZ children, exposure to antibiotics was almost universal; only 3% of children had not been dispensed an antibiotic course by the age of five years. On average, each child received 8 antibiotic courses in the first 5 years of life with the rate of antibiotic dispensing peaking at the end of the first year. Rates of antibiotic dispensing were higher for boys compared with girls, were lower for children living in rural compared with urban regions, and were higher for children of Māori, Pacific, or Asian compared with European ethnicity, and for children living in households of high compared with low socioeconomic deprivation. While direct comparison is difficult due to variations in study methodology, the proportion of children dispensed an antibiotic by year of life and the dispensing incidence rate of 1.9 courses per child per year identified in the current study were high relative to rates reported in recent studies from Europe and the United States (**Table 17**) (53, 176, 184-188).

While the range of antibiotic classes dispensed was similar to that reported in Europe and North America, some differences were evident. Narrow-spectrum penicillins contributed a larger proportion of courses dispensed in NZ and the range of individual medicines dispensed within classes was more limited than that described in the United States (189), Italy (187), and the Netherlands (188). One potential reason for this is that NZ has a central medication purchasing agency, PHARMAC (www.pharmac.govt.nz) which ensures access to key classes of medications but restricts access to multiple closely-related agents. For children, antibiotic choices are also likely to reflect the availability of palatable oral liquid formulations. This explains the low frequency of trimethoprim use compared with trimethoprim-sulfamethoxazole, as no liquid formulation of the former is available in NZ.

Rates of dispensing were low in the first few months of life before increasing relatively rapidly to a peak at one year of age. This finding probably reflects a genuinely lower rate of infection but may in part relate to the data source used. It is likely that general practitioners, faced with an unwell infant at this young age, will be more likely to refer these children to hospital (190) where, for a proportion, antibiotics either are not prescribed or are completed prior to discharge and hence are not included in the dispensing dataset used for this study. Rates of infection could be lower in the youngest infants for several reasons (191). While they are

being cared for at home, young infants may have less exposure to the pathogens which cause the respiratory infections that drive much of the antibiotic prescribing in early childhood (189, 192). They may also have residual passive immunity provided by transplacental transfer of maternal antibody, thus reducing the frequency and severity of illnesses following pathogen exposure during the first few months of life (193).

The finding that antibiotic dispensing peaked at a young age and that 92% of the children were exposed to antibiotics by three years of age, is of concern given current knowledge about the importance of this period of infancy for the establishment of a healthy microbiome. Antibiotic consumption during this critical period may lead to persistent metabolic or immunologic changes (176-178, 194, 195). For example, Bailey *et al*. found that there was an average 11% (RR 1.11, 95% CI 1.02 – 1.21, p=0.02) increase in the risk of obesity for children who had received four or more courses of an antibiotic between ages 0 to 23 months (186). Saari *et al*. also identified significant increases in age-adjusted BMI z-score at 24 months in children who had received antibiotics between ages 0 to 23 months (176). Given these findings, antibiotic exposure could potentially be contributing to childhood overweight and obesity in NZ, and this possibility will be investigated in future research within the GUINZ cohort.

The predominance of amoxicillin use and the pattern of higher dispensing rates in winter are consistent with prior observations of antibiotic prescribing for seasonal respiratory tract infections, the majority of which are caused by viruses (189, 196). Current NZ general practice guidelines recommend expectant management, not antibiotic treatment, for most upper and lower respiratory infections in children (197). However, a previous NZ study found that approximately 75% of children with a self-limited upper respiratory tract infection were prescribed an antibiotic (198). Further research within the GUINZ cohort, including review of general practice electronic records, is being planned to more accurately quantify the reasons for antibiotic prescribing.

Antibiotic prescription rates in general practice also reflect parental healthcare seeking behaviour and beliefs about antibiotics (199-201). A recent multi-country survey conducted by the WHO showed that public knowledge about appropriate antibiotic use is poor (202). While the prescriber is ultimately responsible for the decision to prescribe an antibiotic,

prescribers are influenced by their perceptions of patient expectations for antibiotics (203). Therefore it is important that sufficient educational resources are available to inform parents about when antibiotics are likely to be of use and when they are not, and for general practitioners to address expectations for antibiotics where they perceive them. In NZ, PHARMAC seeks to address this educational need by running an annual campaign during the winter cold and influenza season aiming to reduce demand for antibiotics for these conditions. Our findings emphasise that, although acceptable prescribing guidelines and educational resources have been developed (197), further work is required to reduce unnecessary antibiotic prescribing.

Our study showed that Māori and Pacific children were dispensed a greater number of antibiotic courses. This finding stands in contrast with previous research by from Norris *et al*., which showed that Māori, and particularly rural Māori children, were less likely to be prescribed antibiotics in the community (69), but is consistent with the higher rates of infectious disease morbidity that occur in these population groups (1), and may in part reflect clinicians' awareness of this disparity. The major reasons for the difference between our findings and those of Norris *et al.* are likely to be geographic, as the number of Māori children in GUINZ who lived in rural areas was comparatively small, and the rural areas from which the GUINZ families were recruited were not as remote as the rural areas in the study by Norris *et al.* (69). This likely correlates with lower financial and transportation-related barriers to seeking primary medical care. While we did not identify a statistically significant reduction in access to antibiotics for rural compared with urban Māori children, a trend in this direction was observed. Within the Māori and Pacific ethnic groups, rates of antibiotic dispensing were greatest in children living in the most deprived areas. This suggests that interventions to address high rates of prescribing to Māori and Pacific children could be targeted to those experiencing the most socioeconomic deprivation rather than being applied broadly.

When all ethnicities were considered, children living in rural areas were shown to receive fewer antibiotic courses than children living in urban areas. A number of reasons for this can be hypothesised. Firstly, children in rural communities may lack access to local primary care facilities, particularly outside normal working hours. The need to travel to seek primary care may make rural parents less inclined to seek medical advice for minor ailments (204). Secondly, rural children may have a lower rate of infectious disease due to reduced exposure

to infectious contacts or to immunological differences related to growing up in a rural environment (205). Thirdly, rural children in the cohort were more likely to be of European ethnicity and less likely to be in the most socioeconomically deprived deciles so some degree of unresolved confounding may be occurring.

Key strengths of our study include the large size of the cohort studied, its diverse composition with regard to ethnicity and socioeconomic deprivation, and the high rates of cohort retention and of consent to data linkage. Another major strength is the use of the Pharmaceutical Collection database, which allowed us to accurately quantify antibiotic use without relying on parental recall or individual pharmacy records. Our study also has several important limitations. The number of days of antibiotic dispensed could not be calculated for 19% of antibiotic courses. However, the distribution was tightly clustered around the median of 7 days (IQR 7 – 8 days) so this is likely to be a reliable estimate of central tendency. As antibiotic courses dispensed on separate days were regarded as separate courses, it is possible that a small number of courses dispensed were in fact an extension of the preceding course. However, the higher course count would still reflect a greater degree of antibiotic exposure in this situation. The Pharmaceutical Collection comprises records of dispensing, not consumption, and some courses of antibiotic dispensed will not have been completed. The Pharmaceutical Collection does not include hospital inpatient dispensing or direct supply by a doctor. Some of the cohort children would have received additional antibiotics through these means, although the amounts are likely to be small in comparison with community antibiotic use. In addition, the NZ Ministry of Health does not have a current estimate of the completeness of the Pharmaceutical Collection with regards to community dispensing, although there is a financial incentive for pharmacists to claim every prescription dispensed so the level of completeness is likely to be high. One potential contributor to the high prevalence and incidence figures we have obtained relative to comparable international studies may be that the Pharmaceutical Collection offers a more complete record than other data sources. Despite the high rates described, the limitations of the dataset mean that our results are likely to be an underestimate of total antibiotic exposure.

In conclusion, this study of a large cohort of NZ children has shown high levels of antibiotic dispensing during early childhood. The seasonal pattern of antibiotic dispensing suggests that a large proportion of antibiotic prescribing is for self-limiting respiratory illness. Non-

European children were dispensed more antibiotic courses than European children. This disparity may be due in part to higher rates of infectious disease morbidity in Māori and Pacific children but the proportion of antibiotic prescribing that is unnecessary is likely to be similar to that in children of other ethnicities, and this unnecessary prescribing may have long term consequences for these children including higher rates of antibiotic resistant bacterial infection (22). Interventional studies are required to address the challenges of antimicrobial stewardship in primary care, including addressing parental beliefs and expectations regarding antibiotic use, and doctors' perceptions of the balance of the benefits versus the harms of antibiotic prescribing.

5.5 FIGURES

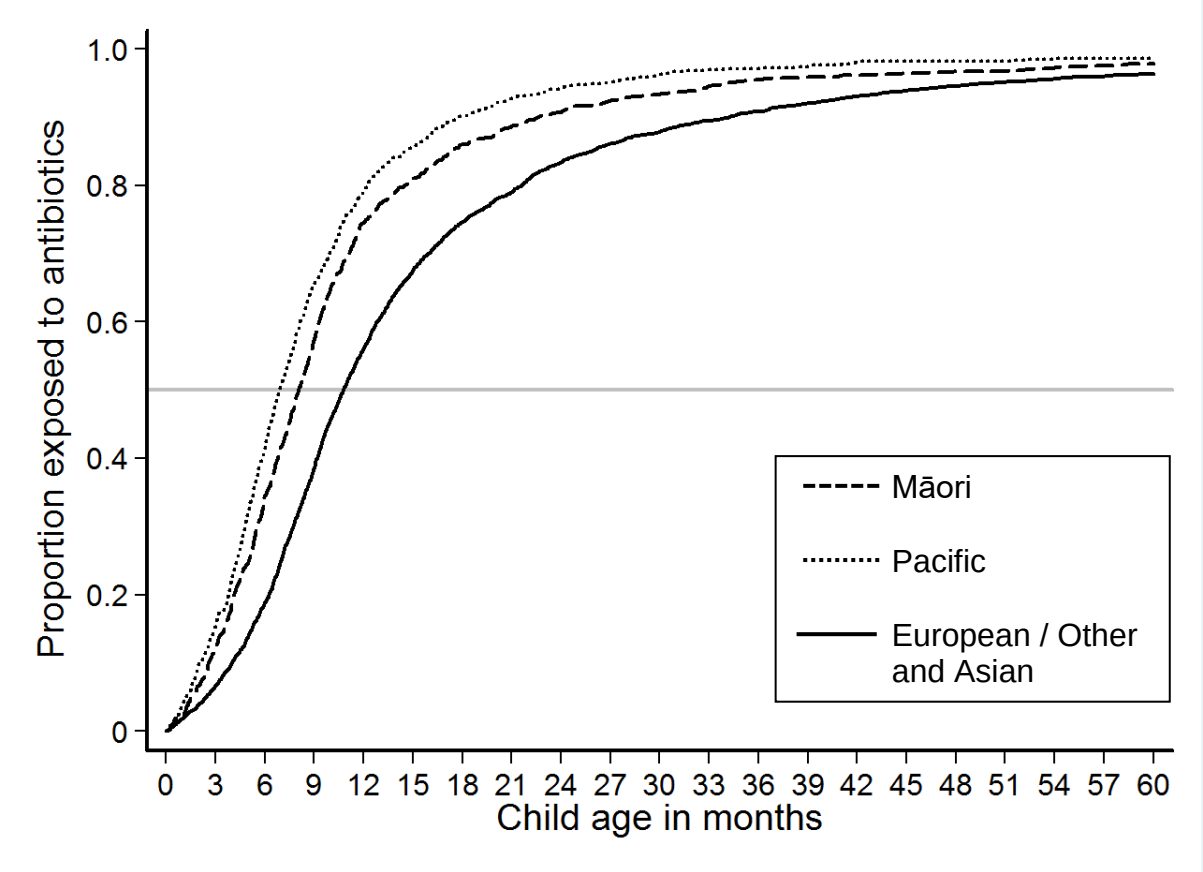

Figure 3: Cumulative distribution function of children dispensed an antibiotic course by child age in months and ethnicity.

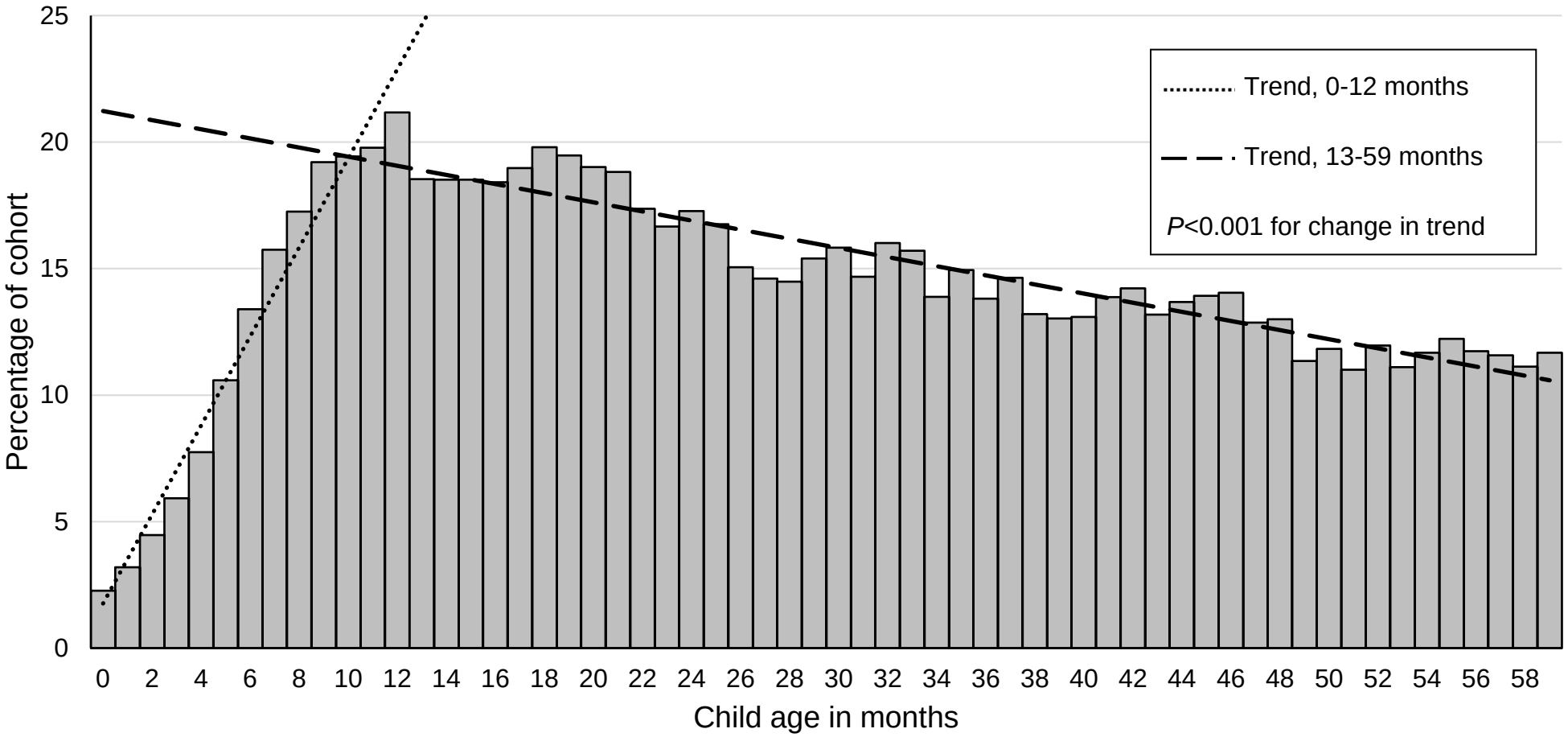

Figure 4: Percentage of 5581 cohort children who were dispensed a course of antibiotic by month of age, from birth to five years

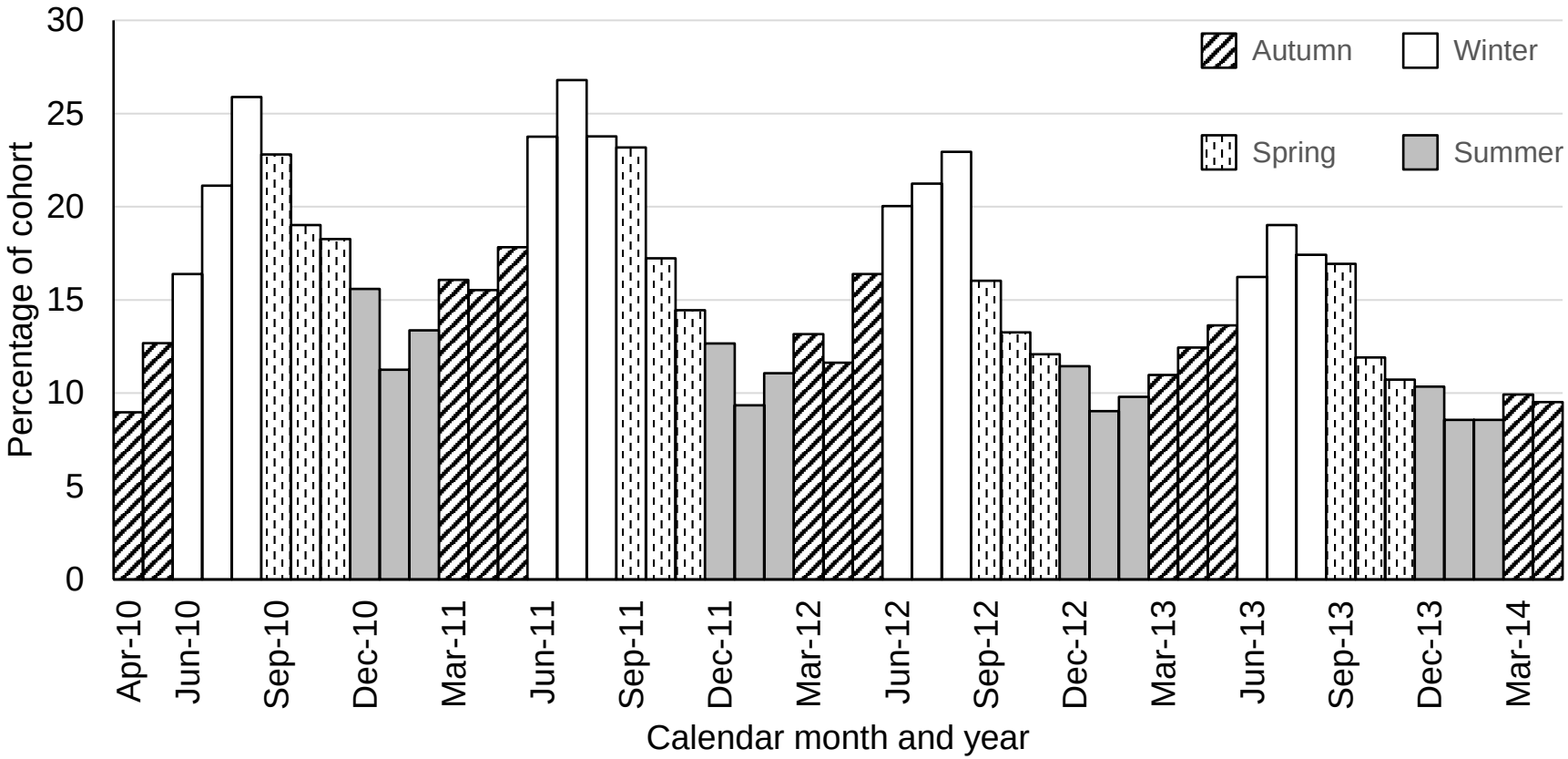

Figure 5: Percentage of 5581 cohort children who were dispensed a course of antibiotic by calendar month and year, restricted to months in which data from the whole cohort was available

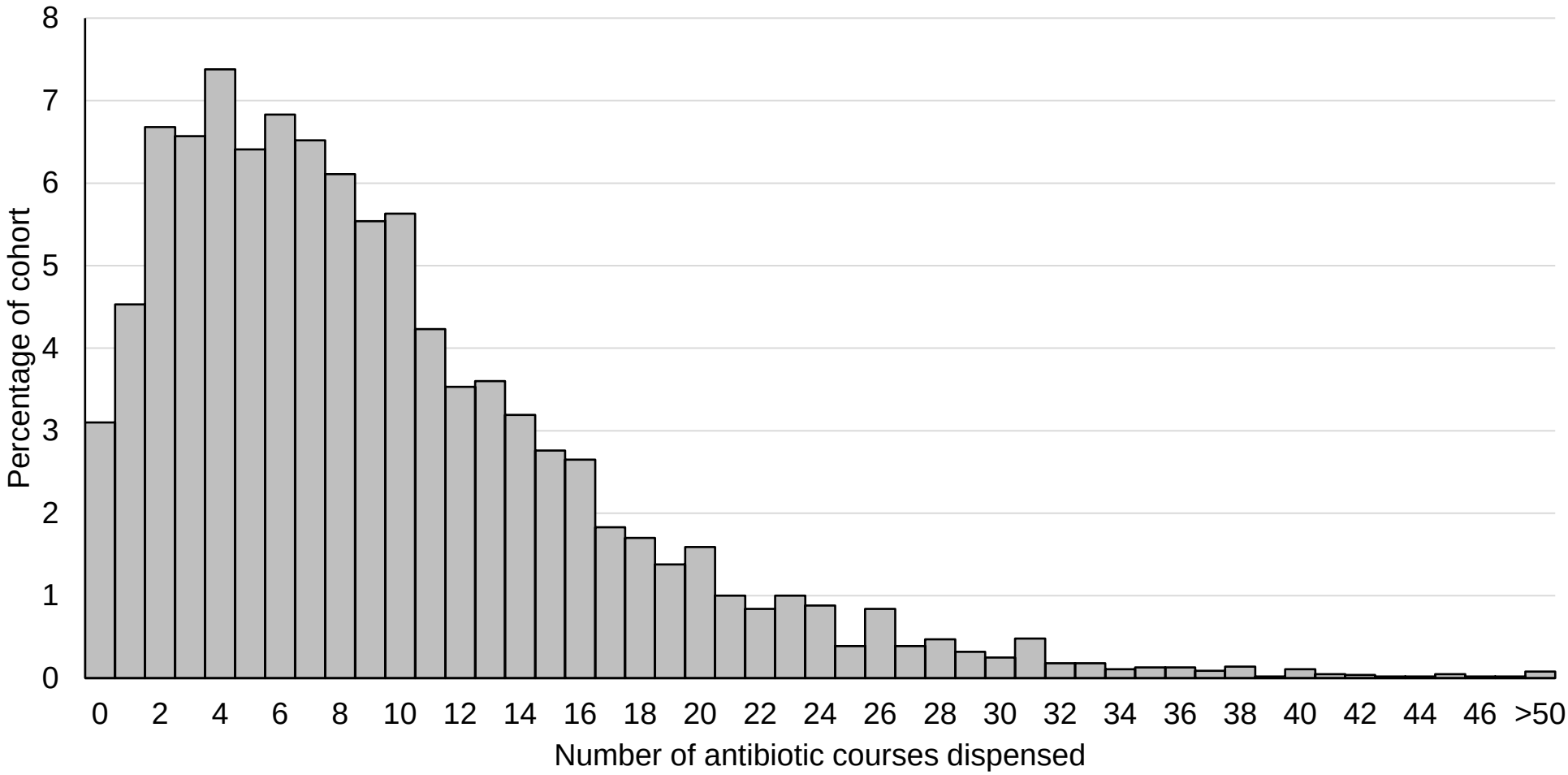

Figure 6: Distribution of the number of antibiotic courses dispensed per child during the first five years of life

5.6 TABLES

Table 11: Antibiotic prescriptions dispensed by class of antibiotic to the 5581 cohort children from birth to age 5 years.

Antibiotic Agent / Class	**Number (%) of antibiotic courses dispensed**
Total	53052 (100)
Penicillins	38724 (73)
Penicillin	899 (2)
Amoxicillin	28813 (54)
Amoxicillin-clavulanic acid	6645 (13)
Flucloxacillin	2367 (4)
Trimethoprim-sulfamethoxazole[a]	5587 (11)
Cephalosporins	5002 (9)
Cefaclor	4207 (8)
Cefalexin	795 (2)
Macrolides[b]	3722 (7)
Other antibiotics[c]	15 (0)

Table 11 Footnote: [a] Includes 2 courses of trimethoprim. [b] Includes 3673 courses of erythromycin, 39 of azithromycin, 8 of roxithromycin, and 1 of clarithromycin. [c] Includes 8 courses of ciprofloxacin, 3 of nitrofurantoin, and 2 each of clindamycin and doxycycline.

Table 12: Proportion of 5581 cohort children who were dispensed one or more antibiotic courses in each year of life, from birth to age 5 years, by ethnic group.

	Percentage of cohort children dispensed one or more antibiotic courses in each year of life, %					**P-value[a]**
Child age in years	**All children (n = 5581)**	**Ethnic group**				
		European / Other (n=3254)	**Māori (n=855)**	**Pacific (n=773)**	**Asian (n=700)**	
<1	62%	56%	75%	79%	53%	<0.001
1	77%	74%	82%	88%	73%	<0.001
2	73%	70%	76%	82%	76%	<0.001
3	70%	66%	74%	77%	77%	<0.001
4	66%	61%	70%	76%	71%	<0.001

Table 12 Footnote: [a] χ^2 test for difference in proportion between ethnic groups

Table 13: Median number of courses of antibiotic dispensed to the 5581 cohort children from birth to age 5 years and unadjusted associations with explanatory variables.

Explanatory variable	**n (%)**	**Median (IQR)**	**P-value[a]**
All children	5581	8 (4 – 13)	
Gender			
Female	2701 (48)	7 (4 – 12)	Reference
Male	2880 (52)	8 (4 – 14)	<0.001
Rurality			
Urban	5047 (90)	8 (4 – 13)	Reference
Rural	533 (10)	6 (3 – 11)	<0.001
Ethnicity			
European / Other	3253 (58)	7 (3 – 11)	Reference
Māori	855 (15)	9 (5 – 15)	<0.001
Pacific	773 (14)	11 (7 – 16)	<0.001
Asian	700 (13)	8 (4 – 13)	<0.001
Deprivation (NZDep2013)			
Low (deciles 1 – 3)	1718 (31)	7 (4 – 12)	Reference
Intermediate (deciles 4 – 7)	2019 (36)	7 (4 – 12)	0.25
High (deciles 8 – 10)	1844 (33)	9 (5 – 15)	<0.001

Table 13 Footnote: [a] Mann-Whitney-Wilcoxon test for pairwise comparison with reference group.

Table 14: Multivariable negative binomial regression of total number of antibiotic courses dispensed to the 5581 cohort children from birth to age 5 years by gender, rural residence, ethnicity, and deprivation group, corrected for birth month

Explanatory variable	**Incidence rate ratio (95% CI)**	**P-value**
Mean at intercept	8.07 (7.72 – 8.43)	
Male gender	1.10 (1.05 – 1.14)	<0.001
Rural residence	0.88 (0.82 – 0.94)	<0.001
Ethnicity		
European / Other	Reference	Reference
Māori	1.29 (1.21 – 1.37)	<0.001
Pacific	1.35 (1.27 – 1.44)	<0.001
Asian	1.07 (1.01 – 1.15)	0.03
Deprivation (NZDep2013)		
Low (deciles 1 – 3)	Reference	Reference
Intermediate (deciles 4 – 7)	0.99 (0.94 – 1.04)	0.69
High (deciles 8 – 10)	1.08 (1.02 – 1.14)	0.009

Table 15: Multivariable negative binomial regression of total number of antibiotic courses dispensed to the 5581 cohort children from birth to age 5 years, stratified by ethnicity and adjusted for gender, socioeconomic deprivation, and rurality.

Explanatory variable	n (%)	IRR (95% CI)	P-value
European/Other ethnicity (n=3253)			
Mean at intercept		8.27 (7.84 – 8.72)	
Deprivation (NZDep2013)			
Low (deciles 1 – 3)	1373 (42)	Reference	Reference
Intermediate (deciles 4 – 7)	1318 (41)	0.95 (0.90 – 1.01)	0.13
High (deciles 8 – 10)	562 (17)	1.05 (0.97 – 1.13)	0.26
Rural residence [a]	444 (14)	0.87 (0.80 – 0.95)	0.001
Māori ethnicity (n=855)			
Mean at intercept		8.42 (7.28 – 9.74)	
Deprivation (NZDep2013)			
Low (deciles 1 – 3)	116 (14)	Reference	Reference
Intermediate (deciles 4 – 7)	252 (29)	1.18 (1.00 – 1.39)	0.04
High (deciles 8 – 10)	487 (57)	1.30 (1.12 – 1.51)	<0.001
Rural residence [a]	81 (9)	0.88 (0.74 – 1.04)	0.13
Pacific ethnicity (n=773)			
Mean at intercept		9.27 (7.59 – 11.32)	
Deprivation (NZDep2013)			
Low (deciles 1 – 3)	43 (6)	Reference	Reference
Intermediate (deciles 4 – 7)	148 (19)	1.14 (0.91 – 1.41)	0.25
High (deciles 8 – 10)	582 (75)	1.26 (1.03 – 1.53)	0.02
Asian ethnicity (n=700)			
Mean at intercept		8.84 (7.85 – 9.96)	
Deprivation (NZDep2013)			
Low (deciles 1 – 3)	186 (27)	Reference	Reference
Intermediate (deciles 4 – 7)	301 (43)	1.09 (0.96 – 1.25)	0.18
High (deciles 8 – 10)	213 (30)	1.03 (0.89 – 1.19)	0.70

Table 15 Footnote: [a] Results for rural residence are only reported for children of European or Māori ethnicity, due to the small numbers in other ethnic groups (<5 each) living in a rural residence

Table 16: Multivariable negative binomial regression of total number of antibiotic courses dispensed to the 5581 cohort children from birth to age 5 years, stratified by deprivation group and adjusted for gender, ethnicity, and rurality.

Explanatory variable	**n (%)**	**IRR (95% CI)**	**P-value**
Low socioeconomic deprivation (NZDep2013 deciles 1 – 3) (n=1718)			
Mean at intercept		8.17 (7.68 – 8.69)	
Ethnicity			
European/Other	1373 (80)	Reference	Reference
Māori	116 (7)	1.07 (0.92 – 1.24)	0.41
Pacific	43 (3)	1.16 (0.91 – 1.48)	0.22
Asian	186 (11)	1.03 (0.91 – 1.17)	0.60
Rural residence	182 (11)	0.93 (0.82 – 1.06)	0.28
Intermediate socioeconomic deprivation (NZDep2013 deciles 4 – 7) (n=2019)			
Mean at intercept		7.95 (7.50 – 8.43)	
Ethnicity			
European/Other	1318 (65)	Reference	Reference
Māori	252 (12)	1.33 (1.20 – 1.48)	<0.0001
Pacific	148 (7)	1.36 (1.19 – 1.54)	<0.0001
Asian	301 (15)	1.15 (1.05 – 1.27)	0.004
Rural residence	284 (14)	0.87 (0.79 – 0.97)	0.008
High socioeconomic deprivation (NZDep2013 deciles 8 – 10) (n=1844)			
Mean at intercept		8.59 (8.02 – 9.20)	
Ethnicity			
European/Other	562 (33)	Reference	Reference
Māori	487 (26)	1.34 (1.23 – 1.46)	<0.0001
Pacific	582 (32)	1.38 (1.27 – 1.49)	<0.0001
Asian	213 (12)	1.01 (0.90 – 1.13)	0.88
Rural residence	67 (4)	0.78 (0.65 – 0.94)	0.007

Table 17: Recent literature reporting paediatric antibiotic prescribing rates, restricted to age stratum most closely matching current study where possible

Author	Pub.	Country	Data source	Period	Age	Incidence (Prescriptions /child/yr)	Prevalence % (period)
Current study	2016	New Zealand	National registry	2009-2015	0-4	1.9	70
Saari *et al.*[11]	2015	Finland	National registry	2003-2007	0-2	NR	76.6 (2 years)
Ternhag *et al.*[27]	2014	Sweden	National registry	2010	0-5	NR	30.2 (1 year)
Holstiege *et al.*[28]	2014	Denmark	Claims DB	2005-2008 [a]	0-4	1.0	NR
"	"	Italy	Claims DB	2007-2008 [a]	0-4	1.4	NR
"	"	Germany	Claims DB	2005-2008 [a]	0-4	0.9	NR
"	"	Netherlands	Pharmacy DB	2005-2008 [a]	0-4	0.5	NR
"	"	UK	Primary care DB	2005-2008 [a]	0-4	0.8	NR
Bailey *et al.*[29]	2014	USA	Primary care DB	2001-2013	0-2	NR	69 (2 years)
Clavenna *et al*.[30]	2009	Italy	Prescription DB	2006	0-14	NR	52.4 (1 year)
De Jong *et al.*[31]	2008	Netherlands	Pharmacy DB	1999-2005	0-4	0.3	29 (1 year)
Hall *et al.*[2]	2002	New Zealand	Primary care DB	1998-1999	0-6	1.6	NR

Table 17 Footnote: NR = not reported. [a] Only 2008 results presented from Holstiege *et al*. paper. Results for Italian region only available from 2007-2008.

CHAPTER 6: HOSPITALISATIONS FOR INFECTIOUS DISEASE DURING THE FIRST FIVE YEARS OF LIFE IN NEW ZEALAND CHILDREN

Chapter 5 identified that children in NZ are prescribed antibiotics at a high rate when compared with other developed countries, and that Māori and Pacific children, and those living in more socioeconomically deprived areas, receive more antibiotics than others. This disparity may in part have reflected the burden of community ID as well as the quality of primary care received.

This chapter describes hospitalisations for infectious disease up to the age of five years and examines the determinants of reduced access to primary healthcare and how reduced access to healthcare affects the rate of hospitalisation. Hospitalisations for infectious disease were found to be common, affecting over 25% of the cohort. Māori and Pacific children were more likely to have experienced reduced access to primary healthcare, and to have experienced hospitalisation for an infectious disease. Reduced access to primary healthcare was itself independently associated with an increased risk of hospitalisation for an infectious disease. The list of the most common diagnoses includes some potentially serious infections such as bronchiolitis and pneumonia – improved access to primary care would not necessarily be expected to prevent these admissions.

6.1 INTRODUCTION

New Zealand (NZ) children experience high rates of hospitalisation for infectious diseases (ID), estimated at 9108 hospitalisations per 100,000 children per year for children under five years of age in 2004-2008 (1). Furthermore, rates amongst these children increased by 22% between 1989 and 2008 (1). Similar increases have been reported in England and Denmark (206, 207), particularly for hospitalisations of less than 24 hours' duration. While some of these brief hospitalisations will have been unavoidable, others may have been preventable by timely access to primary healthcare (206, 208).

Significant ethnic and socioeconomic inequalities can be seen in rates of hospitalisation for ID in NZ (1, 3), and these inequalities are worsening. Between 1989 and 2008, the age-standardised rate ratios of ID hospitalisation increased 27.6% and 48.3% for Māori and Pacific children under five respectively, compared with European children (1). Both Māori and Pacific peoples suffer disproportionate exposure to adverse social determinants of health such as socioeconomic deprivation and household crowding. Studies in Australia and the USA have also shown higher rates of ID amongst socioeconomically disadvantaged minority and indigenous populations when compared with the ethnic majority population (80, 94). However, differences in economic status appear to only partially explain the observed disparities in health outcomes. Recent research in NZ has shown that access to healthcare (208, 209) and experience of racism (135, 136) also influence health status significantly.

There is an urgent need to better understand the factors leading to ethnic disparities in childhood ID hospitalisations, in NZ and in other developed nations, in order to inform interventions aiming to reduce the disparities in health outcomes experienced by marginalised populations. We hypothesised that Māori and Pacific children would be more likely to have had reduced access to primary care, and that children with reduced access to primary care would be more likely to be hospitalised for an ID by the age of five years. Thus, the objectives of this study were to quantify the period prevalence of hospitalisation for an ID in the first five years of life; and to examine the effects of ethnicity and access to primary healthcare on this outcome.

6.2 METHODS

6.2.1 Study design, population and sample

This study was conducted within the *Growing Up in New Zealand* (GUINZ [www.growingup.co.nz]) longitudinal child cohort study, using data from caregiver interviews and from linkage to national administrative health datasets. GUINZ enrolled 6853 children from a geographical region defined by the contiguous Auckland, Counties-Manukau, and Waikato District Health Board areas over 12 months in 2009-2010. The enrolled cohort included 11% of the national and 33% of the regional birth cohort. The study oversampled Māori and Pacific mothers to obtain a child cohort that is generalisable to the NZ national birth cohort with regards to ethnic and socioeconomic diversity (37-39).

6.2.2 Ethics

Ethical approval was provided by the Ministry of Health Northern Y Regional Ethics Committee. Written informed consent was sought from each child's primary caregiver.

6.2.3 Data collection and linkage

Interviews were conducted with the primary caregiver in the antenatal period, and when the child was 9 months, and 2 and 4½ years old. Linkage was established with birth hospital perinatal records, the National Immunisation Register (NIR) (42), and the National Minimum Dataset (NMDS) (41). using each child's unique National Health Index number. The NIR records the receipt of scheduled childhood immunisations (42).

The NMDS contains information on all public hospitalisations in NZ, including emergency department attendance and day-case surgeries, but not outpatient clinic consultations (41). All acute paediatric hospitalisations in NZ are to public hospitals, and are free of charge for citizens and permanent residents. The NMDS includes discharge diagnoses, coded using the Australian Modification of the International Classification of Diseases and Health Related Problems (ICD-10-AM). The first listed ICD-10-AM code represents the main health problem managed during the hospitalisation. A day of hospitalisation is defined in the NMDS as bed

occupancy at midnight – thus zero-day hospitalisations represent an emergency department or inpatient ward attendance without an overnight stay.

6.2.4 Outcome variables

The primary outcome of interest was hospitalisation for an ID during the first five years of life. Reduced access to healthcare was investigated both as a secondary outcome and as an explanatory variable.

Hospitalisations for an ID were identified by recoding ICD-10-AM discharge diagnostic codes. Only the first diagnostic code was considered with the aim of capturing only hospitalisations which were primarily for an ID. Birth hospitalisations and hospitalisations for non-medical reasons (e.g. maternal hospitalisation) were excluded. Hospitalisations for infective exacerbations of a chronic condition, such as asthma or eczema, were included but hospitalisations for non-infective sequelae of an ID were not included (**Table 18**).

Reduced access to healthcare was defined as the child having been unable to see a doctor and/or obtain prescribed medicines when required. Caregivers were asked at 9 months, and at 2 and 4½ years, whether this had occurred in the preceding year. We did not define incomplete or delayed vaccination as a lack of access to healthcare, firstly because the number of children with delayed vaccination was significantly greater than the number of children with reduced access to healthcare as otherwise defined, and secondly because parental choice is a common reason for delayed or incomplete vaccination and is not related to socioeconomic status in NZ (210).

6.2.5 Explanatory variables

Explanatory variables were obtained from caregiver interviews and included: the child's ethnicity and sex; maternal age and educational attainment; gestational age at delivery, birthweight, mode of delivery and total breast feeding duration; household socioeconomic

status, presence and type of heating, tobacco smoke exposure, crowding, rurality, and transience; access to healthcare; and maternal experience of racism in a healthcare setting.

Children in the cohort commonly have more than one ethnicity (39, 155). To maintain subgroup size and statistical power and to allow comparison between ethnic groups, each child's primary caregiver was asked to identify their child's single principal ethnicity at the 4½ year interview. Ethnicity was analysed in broad categories: Māori, Pacific, Asian, and European/Other. The European/Other ethnic group was used as the reference group due to its large size and the intention to demonstrate the disparities in health outcomes for Māori and Pacific children.

The mother's highest educational attainment was determined in the antenatal period, and categorised either as high-school level or below, or as any tertiary qualification (diploma or degree). Preterm birth was defined as delivery prior to 37 weeks of gestation. Low birthweight was considered only in infants born after 37 weeks gestation and was defined as birthweight less than 2500 g. Mode of delivery was categorised as normal or assisted vaginal delivery vs. caesarean delivery. Total breastfeeding duration was defined as any feeding of breast milk, with or without other foods or infant formula, and categorised as having stopped at <6 months or ≥6 months of child age.

Using data from the NIR, we defined immunisation completeness as receipt of all scheduled immunisations before the age of 1 year, and timeliness as receipt within 30 days of their scheduled date.

Socioeconomic deprivation was assessed using the NZiDep, a validated, individualised deprivation scale derived from responses to 8 questions regarding employment, receipt of government benefits or charity, and the need to save money on food, heating, or footwear, with responses scored from 1 (least deprived) to 5 (most deprived) (51). We defined exposure to socioeconomic deprivation as an NZiDep score of ≥3 at either or both of the 9 month or 4½ year interviews. Based on previous research (131), variables describing a lack of household

heating and use of gas heating in the child's room at 9 months were included. Household smoking was defined as tobacco smoking by any member of the child's household. Household crowding was defined as a ratio of occupants to bedrooms of >2. Rural residence was defined as classified by Statistics New Zealand (49). Household transience was defined as having moved house 4 or more times in the child's first five years of life. Maternal experience of racism in a healthcare setting was defined as the reported experience of discrimination on the basis of skin colour or ethnicity from a healthcare provider.

Explanatory variables including the NZiDep, household smoke exposure, crowding and rurality, reduced access to healthcare, and maternal experience of racism were measured at multiple data collection waves. Following exploratory data analysis, these exposures were reduced to binary categorical variables, and analysed as ever exposed vs. never exposed.

6.2.6 Statistical analysis

SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for data management and analyses. Analyses were restricted to cohort children for whom complete data were available. Unadjusted associations were assessed using risk ratios, 95% confidence intervals, and p-values derived from the Fisher's exact or χ^2 tests, then confirmed using bivariate log-binomial models. Multivariable analyses were performed using log-binomial regression models, with results presented as adjusted risk ratios, 95% confidence intervals, and p-values. Log-binomial regression was used to directly derive risk ratios as the primary outcome was not rare and odds ratios would therefore overestimate the true risk ratio (211). Multivariable models were built with and without ethnicity variables, and within each ethnic subgroup. Models included all explanatory variables with an unadjusted p-value of ≤ 0.15. It was decided *a priori* that sex and socioeconomic deprivation would be retained regardless of significance. As the intention was to generate descriptive rather than predictive models, models were built using the whole cohort rather than training and testing sub-cohorts. The log-binomial model for the European/Other ethnic group failed to converge, a known problem with log-binomial models (211), so a Poisson model with the dispersion parameter estimated by Pearson's χ^2 divided by the degrees of freedom was used this ethnic group.

6.3 RESULTS

Ninety percent (6156/6853) of cohort participant caregivers completed the interview at 4½ years of child age, and 92% (5670/6156) of these caregivers provided consent to access administrative health data. Four children were excluded due to linkage mismatch. Linkage was established for the remaining 5666. Analyses were restricted to 5484 children for whom data was complete.

Of these 5484 children, 1401 (25.6%) had experienced a total of 2221 hospitalisations for an ID in their first five years of life. In addition, 1693/5484 (30.9%) of the cohort children experienced a total of 2849 non-ID hospitalisations, including 602 (11.0%) children who experienced both ID and non-ID hospitalisations. The number of children who experienced one or more hospitalisations in their first five years of life and the number of hospitalisations they experienced are shown in **Table 19**. The most common individual diagnostic codes are listed in **Table 20**.

Hospitalisation for an ID was most common in the first year of life with 919/2221 (41.4%) occurring before the child's first birthday. A seasonal pattern driven largely by respiratory infections was observed, with 787/2221 (35.4%) of the hospitalisations for an ID occurring during the winter (June-August) compared with 369 (16.6%) during the summer (December-February) ($p<0.001$) (**Figure 5**).

Hospitalisations for an ID tended to be short with a median length of stay of 1 day (interquartile range 0-2 days). The recorded length of stay was zero days for 935/2221 (42.1%), 1 day for 579/2221 (26.1%), 2 days for 282/2221 (12.7%) and 3 days or longer for 425/2221 (19.1%).

Of the 1401 children who had experienced one or more hospitalisations for an ID, 950 (67.8%) experienced one, and 278 (19.8%), 98 (7.0%), and 75 (5.4%) children experienced two, three, or four or more hospitalisations respectively. Of these 451 children with repeated hospitalisations, 210 (46.6%) had more than one hospitalisation for a respiratory infection. Of

2221 hospitalisations for an ID, 176 (7.9%) were within 14 days of discharge from a preceding hospitalisation for an ID.

Reduced access to healthcare was experienced by 718 (13.1%) children – 198/824 (24.0%) Māori, 153/727 (21.1%) Pacific, 58/624 (8.5%) Asian, and 309/3251 (9.5%) European/Other children (P<0.001). Associations with reduced access to healthcare are listed in **Table 21**. The multivariable model showed that reduced access to healthcare was associated with Māori or Pacific ethnicity, lower maternal educational attainment, a shorter duration of breast feeding, socioeconomic deprivation, household smoking, and maternal experience of racism in healthcare. The reasons for reduced access to healthcare are shown in **Table 22**.

Children with reduced access to healthcare were more likely to experience hospitalisation for an ID (34.5% vs. 24.2%, RR 1.43, 95% CI 1.28 – 1.60, P<0.001), and to experience multiple hospitalisations for ID (13.4% vs. 7.5%, RR 1.79, 95% CI 1.45 – 2.22, P<0.001). Within the subset of children who had experienced one or more hospitalisations for an ID, children with reduced access to healthcare were more likely to have had multiple hospitalisations (38.7% vs. 30.8%, RR 1.26, 95% CI 1.05 – 1.50, P=0.02) but were not more likely to have had one or more brief, 0-day length of stay hospitalisations (50.0% vs. 55.5%, RR 0.90, 95% CI 0.79 – 1.03, P=0.11).

Associations between the explanatory variables and having had one or more hospitalisations for an ID before age 5 years, are shown in **Table 23**. When ethnicity was included, the multivariable model showed that Māori or Pacific ethnicity, male sex, younger maternal age, preterm birth, low birthweight at term, shorter duration of breast feeding, socioeconomic deprivation, a lack of household heating and use of gas heating in the child's bedroom, reduced access to healthcare, and maternal exposure to racism in a healthcare setting were associated with a higher risk of hospitalisation for an ID. Rural residence was associated with a lower risk of hospitalisation for an ID. When ethnicity was excluded from the multivariable model, household crowding became significantly associated with a higher risk of hospitalisation for an ID (despite meeting criteria for removal from the previous model) and small increases were observed in the effect size of other variables describing the household

environment. Supplementary results are presented using total-response ethnicity, in which overlap between ethnic groups is allowed, in **Table 24**.

When multivariable analyses were performed within ethnic subgroups (**Tables 25-28**), the variables associated with a higher risk of hospitalisation for an ID differed between ethnic groups. For European/Other children, the variables associated with an increased risk of hospitalisation for an ID were similar to those seen in the whole cohort with the exception of maternal exposure to racism in a healthcare setting. For Māori children, a higher risk of hospitalisation for an ID was associated with male sex, younger maternal age, caesarean delivery, a lack of household heating, and maternal exposure to racism in a healthcare setting. For Pacific children, a higher risk of hospitalisation for an ID was associated with younger maternal age, shorter duration of breast feeding, socioeconomic deprivation, and a lack of household heating.

6.4 DISCUSSION

This study, conducted within a diverse and generalisable cohort of NZ children, showed that hospitalisations for ID are common in children under five years of age. One quarter of the children had a hospitalisation for an ID, with the highest incidence in the first year of life and a rapid decline during the subsequent four years. Just under a third of the children who had a hospitalisation for an ID had repeated hospitalisations, often for repeated respiratory illness with the attendant risk of long-term consequences including bronchiectasis. Over half of all hospitalisations for an ID were for respiratory infections, which contributed to a significant seasonal variation in hospitalisation rates.

Consistent with our hypotheses and with previous studies, we identified marked ethnic disparities in the period prevalence of hospitalisation for an ID in NZ, with Māori and Pacific children being more affected than Asian and European/Other children (1, 3, 6, 14). In addition, Māori and Pacific children were more likely to have experienced reduced access to healthcare,

were more likely to be exposed to adverse social determinants of health, and were more likely to have mothers who reported experiencing racism in a healthcare setting.

Reduced access to healthcare was in turn independently associated with socioeconomic deprivation and with maternal experience of racism in a healthcare setting. The reduced access to healthcare variable encompasses a variety of reasons for lack of access including transport, opening hours, competing time commitments, and financial barriers to accessing care, not all of which are amenable to intervention from within the healthcare system. In NZ, prescribed medications and primary care visits to the practice at which the child is registered are free of charge. However, after-hours medical care in NZ is seldom provided by the patient's registered general practice but instead by accident and medical practices which, at the time of this study, would usually have charged consultation fees for children (after-hours care for children became free of charge in 2015). Public hospital care is however free of charge to citizens and permanent residents. Previous studies have suggested that lack of access to primary care has been a cause for increasing numbers of potentially preventable brief hospitalisations for 'primary-care sensitive' conditions (206, 208), and Māori and Pacific New Zealanders have been shown to experience high rates of these avoidable events (212). NZ data have also shown that a lack of access to timely primary care, particularly outside normal working hours, was a commonly cited reason for self-presentation to the hospital emergency department (213, 214).

Maternal exposure to racism in a healthcare setting was found to be independently associated with risk of hospitalisation for an ID for Māori children and within the cohort as a whole. This is consistent with NZ and international research indicating that racial discrimination has a significant role in mediating ethnic disparities in health outcomes (8, 135, 215). Racism is believed to affect health outcomes through a variety of pathways including differences in access to healthcare, the quality of care received, and broader issues regarding the distribution of the social determinants of health, and the effects of exposure to violence and stress (125, 136, 216).

Marked ethnic disparities in the social determinants of health were identified, and it is likely that confounding between ethnicity and socioeconomic factors accounts for some of the

observed disparities in ID rates. As an example, the relationship between ethnicity and household crowding, an established risk factor for communicable disease (127), is of particular interest. Exposure to crowding was associated with hospitalisation for an ID in the unadjusted analysis (RR 1.56, 95% CI 1.43 – 1.71) but not in the multivariable model with ethnicity included. When ethnicity was excluded, crowding remained significant (RR 1.22, 95% CI 1.11 – 1.35). This is likely due to unresolved confounding between crowding and ethnicity, as 70.7% of Pacific children were exposed to household crowding compared with 43.5% of Māori, 43.0% of Asian and 13.5% of European/Other children.

While we suggest that unresolved confounding due to the confluence of multiple ethnic disparities in exposure to the social determinants of health is likely to explain much of the ethnic disparity in ID rates, unmeasured ethnic differences in factors which influence the quality of healthcare received, such as health literacy and doctor behaviour, may also affect hospitalisation rates. For example, if doctors are aware of high rates of serious ID amongst Māori and Pacific children they may have a lower threshold for hospital referral.

Strengths of this study included the size and diversity of the cohort, high retention and linkage consent rates, and the ability to link to hospital discharge records. Nevertheless, this study had some limitations. Diagnostic coding in the NMDS is dependent on the accuracy of data provided by the contributing hospitals and has been estimated to be accurate to the third ICD-10 code digit in 85.8% of cases (217). Our use of broad categories such as 'respiratory infections' has meant that this level of accuracy is adequate for this study. The NMDS does not include information on illness severity, beyond the diagnostic codes. As our intention was to describe the total burden of hospitalisation for ID, including unnecessary hospitalisations for minor conditions, this was acceptable. We used only the first diagnostic code which could have led to an underestimate of the proportion of hospitalisations for which infection was a significant contributor. However, we identified only a small number of children, 117 (2.1%), who had a hospitalisation with a non-ID first diagnostic code and an ID second code, and no other hospitalisations for an ID. Many exposure variables measured at several time points were categorised as ever vs. never exposed. While this limited our ability to comment on the duration of exposure, it maintained the size and statistical power of exposure groups and appeared appropriate from preliminary exploratory data analysis.

In summary, we have demonstrated significant ethnic disparities in rates of hospitalisation for an ID in NZ children, and that these are in large part related to the unequal distribution of the social determinants of health including socioeconomic deprivation, access to healthcare, and racism. These findings are important for children in NZ and elsewhere, as they illustrate a number of factors amenable to intervention. The experience of racism by some healthcare system users must be addressed, and access to primary healthcare for children improved. Action is also required to address socioeconomic deprivation in families. Ethnic-specific interventions may be appropriate to address the ID disease burden within different ethnic groups. Further research is required to address the contribution of unmeasured factors such as health literacy and variance in health professional behaviours to ethnic disparities in health outcomes.

6.5 FIGURES

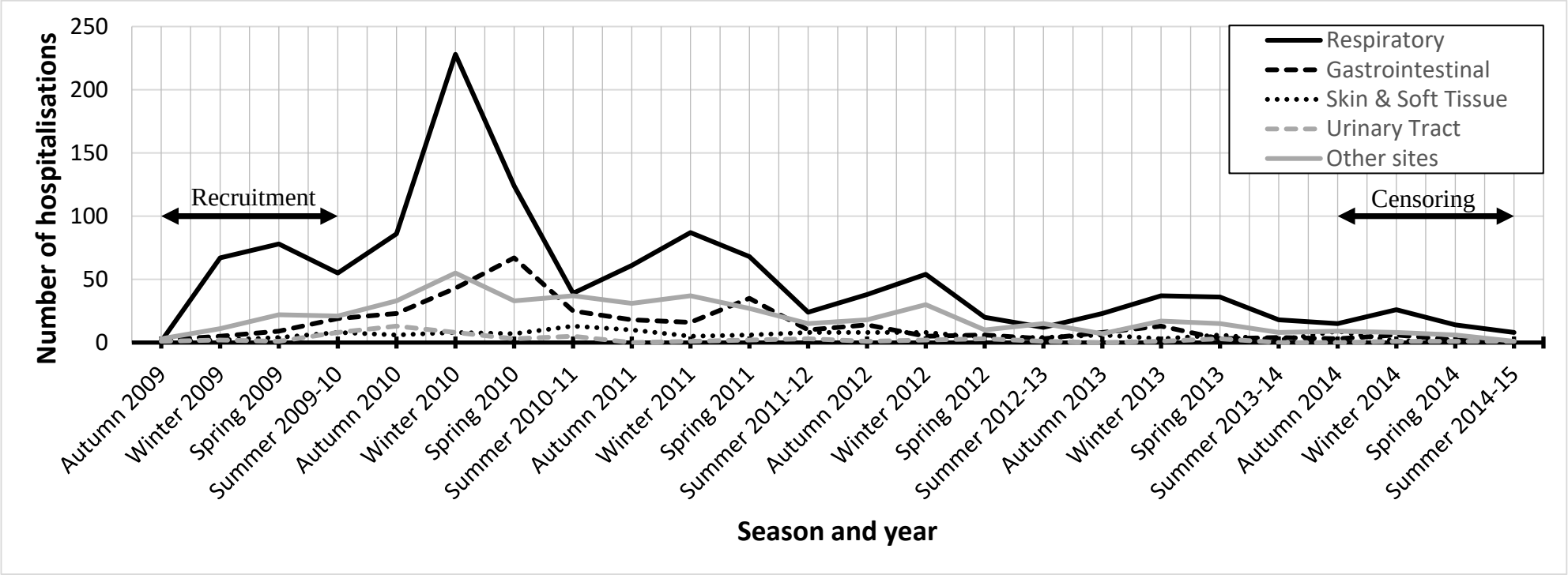

Figure 7: Number of hospitalisations for an infectious disease experienced by 5484 children, by season, year, and admission type.

Cohort recruitment occurred between autumn 2009 and autumn 2010, and hospitalisations after the child's fifth birthday were censored (beginning autumn 2014), therefore the cohort was less than the full 5484 during these times.

6.6 TABLES

Table 18: List of Australian Modification of the International Classification of Diseases and Health Related Problems (ICD-10-AM) codes used to identify infectious disease hospitalisation by recoding the first diagnostic code for that hospitalisation. ICD-10-AM codes differ from standard ICD-10 codes in not having a decimal point prior to the third digit.

Infection type	**ICD-10-AM codes**
Respiratory infections, including ear, nose and throat, and dental infections	A360, A361, A362, A363, A368, A369, H660, H661, H662, H663, H664, H669, H670, H671, H678, H830, J00, J010, J011, J012, J013, J014, J018, J019, J020, J028, J029, J030, J038, J039, J040,J041, J042, J043, J050, J051, J060, J068, J069, J09, J100, J101, J108, J111, J112, J118, J36, J390, J391, K044, K046, K047, K050, K052, K112, K113, K122, J200, J201, J202, J203, J204, J205, J206, J207, J208, J209, J210, J211, J218, J219, J22, J40, J440, J47, A370, A371, A378, A379, A481, B371, B440, B441, B450, B460, B59, J100, J110, J120, J121, J122, J123, J128, J129, J13, J14, J150, J151, J152, J153, J154, J155, J156, J157, J158, J159, J160, J168, J17, J180, J181, J182, J188, J189, J850, J851, J852, J853, J860, J869
Gastro-intestinal / intra-abdominal infections	A020, A030, A031, A032, A033, A038, A039, A040, A041, A042, A043, A044, A045, A046, A047, A048, A049, A050, A052, A053, A054, A058, A059, A071, A072, A080, A081, A082, A083, A084, A085, A090, A099, K350, K351, K352, K353, K3580, K3589, K359, K36, K37, K570, K572, K574, K578, K610, K611, K612, K613, K630, K631, K650, K659, K670, K671, K672, K673, K750, K800, K803, K804, K810, K819, K822, K830, K832
Genitourinary infections	N10, N11, N110, N111, N119, N12, N136, N300, N308, N309, N340, N390, N410, N412, N419, T835, T836
Skin and soft tissue infections	A260, A269, A46, B86, H000, H001, H031, H038, H050, H600, H601, H602, H603, H609, H610, H620, H622, H623, H624, L01, L010, L011, L02, L020, L021, L022, L023, L024, L028, L029, L03, L030, L0301, L0302, L031, L0310, L0311, L032, L033, L038, L039, L04, L040, L041, L042, L043, L048, L049, L050, L08, L080, L081, L088, L089, L303, N482, N499, N61, N764
Other infection types	A021, A022, A028, A029, A051, A250, A251, A259, A270, A278, A279, A280, A281, A282, A288, A289, A300, A301, A302, A303, A304, A305, A308, A309, A310, A311, A312, A318, A319, A320, A327, A3281, A329, A380, A381, A388, A389, A401, A403, A408, A409, A411, A412, A413, A414, A415, A4151, A418, A419, A420, A421, A422, A427, A428, A429, A430, A431, A438, A439, A440, A441, A448, A449, A480, A482, A483, A484, A485, A488, A491, A492, A493, A498, A499, A500, A501, A502, A503, A504, A505, A506, A507, A509, A510, A511, A512, A513, A514, A515, A519, A520, A521, A522, A523, A527, A528, A529, A530, A539, A540, A541, A542, A543, A544, A545, A546, A548, A549, A55, A560, A561, A562, A563, A564, A568, A57, A58, A590, A598, A599, A600, A601, A609, A630, A638, A64, A65, A660, A661, A662, A663, A664, A665, A666, A667, A668, A669, A670, A671, A672, A673, A679, A680, A681, A689, A690, A691, A692, A698, A699, A70, A710, A711, A719, A740, A748, A749, A810, A810, A811, A812, A818, A819, A820, A821, A829, A830, A831, A832, A833, A834, A835, A836, A838, A839, A840, A841, A848, A849, A850, A851, A852, A858, A86, A880, A881, A888, A89, B000, B001, B002, B004, B005, B007, B008, B009, B03, B04, B070, B078, B079, B080, B081, B082, B083, B084, B085, B086, B087, B088, B09, B100, B108, B170, B171, B172, B178, B179, B182, B188, B189, B190, B192, B199, B20, B250, B251, B252, B258, B259, B270, B271, B278, B279, B300, B301, B302,

Table 18 continued Other infection types	B303, B308, B309, B330, B332, B333, B338, B340, B341, B342, B343, B344, B348, B349, B350, B351, B352, B353, B354, B355, B356, B358, B359, B360, B361, B362, B363, B368, B369, B370, B372, B373, B374, B376, B377, B378, B379, B420, B421, B427, B428, B429, B430, B431, B432, B438, B439, B442, B447, B448, B449, B451, B452, B453, B457, B458, B459, B461, B462, B463, B464, B465, B468, B469, B470, B471, B479, B480, B481, B482, B483, B484, B488, B49, B581, B582, B583, B588, B589, B601, B602, B608, B64, B951, B952, B953, B954, B955, B957, B958, B960, B961, B962, B963, B964, B965, B966, B967, B968, B970, B971, B972, B973, B974, B975, B976, B977, B978, B998, B999, E060, G060, G061, G062, G07, G08, H043, H061, H100, H131, H190, H191, H192, H220, H320, H440, H451, H610, H622, H623, H624, H940, I301, I330, I339, I38, I39, I390, I391, I392, I393, I394, I398, I400, I41, I410, I411, I412, I430, I520, I521, I681, I880, I888, I889, K770, L050, M600, M630, M631, M632, N34, N340, N341, N342, N343, N45, N450, N459, N482, N49, N490, N491, N492, N498, N499, N510, N511, N512, N61, N70, N700, N701, N709, N71, N710, N711, N719, N72, N730, N731, N732, N733, N734, N735, N738, N739, N74, N751, N760, N761, N762, N763, N770, N771, O753, O85, O86, O860, O861, O862, O863, O864, O868, O91, O910, O911, O912, O98, O980, O981, O982, O983, O984, O985, O986, O987, O988, O989, R75, R50, R508, R509, R560, R572, R650, R651, T802, T814, T826, T827, T857, T874, T880, Z21, Z22, Z220, Z221, Z222, Z223, Z224, Z225, Z226, Z228, Z229, A321, A390, A391, A392, A393, A394, A395, A398, A399, A870, A871, A872, A878, A879, B003, B375, G000, G001, G002, G003, G008, G009, G01, G020, G021, G028, G032, G042, G050, G051, G052, R835, A33, A34, A35, A360, A361, A362, A363, A368, A369, A800, A801, A802, A803, A804, A809, B010, B011, B012, B018, B019, B020, B021, B022, B023, B027, B028, B029, B050, B051, B052, B053, B054, B058, B059, B060, B068, B069, B160, B161, B162, B169, B180, B181, B191, B260, B261, B262, B263, B268, B269, M014, P350, A000, A001, A009, A010, A011, A012, A013, A014, A060, A061, A062, A063, A064, A065, A066, A067, A068, A069, A070, A073, A078, A079, A200, A201, A202, A203, A207, A208, A209, A210, A211, A212, A213, A217, A218, A219, A220, A221, A222, A228, A229, A230, A231, A232, A233, A238, A239, A240, A241, A242, A243, A249, A750, A751, A752, A753, A759, A770, A771, A772, A773, A774, A778, A779, A78, A790, A791, A798, A799, A90, A91, A920, A921, A922, A923, A924, A928, A929, A930, A931, A932, A938, A94, A950, A951, A959, A960, A961, A962, A968, A969, A980, A981, A982, A983, A984, A985, A988, A99, B150, B159, B331, B334, B380, B381, B382, B383, B384, B387, B388, B389, B390, B391, B392, B393, B394, B395, B399, B400, B401, B402, B403, B407, B408, B409, B410, B417, B418, B419, B500, B508, B509, B510, B518, B519, B520, B528, B529, B530, B531, B538, B54, B550, B551, B552, B559, B560, B561, B569, B570, B571, B572, B573, B574, B575, B580, B600, B650, B651, B652, B653, B658, B659, B660, B661, B662, B663, B664, B665, B668, B669, B670, B671, B672, B673, B674, B675, B676, B677, B678, B679, B680, B681, B689, B690, B691, B698, B699, B700, B701, B710, B711, B718, B719, B72, B730, B731, B740, B741, B742, B743, B744, B748, B749, B75, B760, B761, B768, B769, B770, B778, B779, B780, B781, B787, B789, B79, B810, B811, B812, B813, B814, B818, B820, B829, B830, B831, B832, B833, B834, B838, B839, B870, B871, B872, B873, B874, B878, B879, B880, B881, B882, B883, B888, B889, B89, H130, K931, P373, P374, A150, A151, A152, A153, A154, A155, A156, A157, A158, A159, A160, A161, A162, A163, A164, A165, A167, A168, A169, A170, A171, A178, A179, A180, A181, A182, A183, A184, A185, A186, A187, A188, A190, A191, A192, A198, A199, K930, M490, M900, N740, N741, P370, H700, H701, H702, H708, H709, H750, K102, M00, M000, M001, M002, M008, M0085, M009, M0095, M0096, M0097, M01, M010, M011, M012, M013, M014, M015, M016, M018, M462, M463, M464, M465, M490,M491, M492, M493, M86, M860, M861, M862, M863, M864, M865, M866, M868, M8685, M8687, M869, M8694, M8695, M8696, M8697, M8698, M900, M901, M902, T845, T846, T847, A410, A490, B956, J152, L00, M000, A400, B950, I00, I010, I011, I012, I018, I019, I020, I029, L540, M303, P002, P027, P23, P230, P231,

Table 18 continued Other infection types	P232, P233, P234, P235, P236, P238, P239, P35, P350, P351, P352, P353, P358, P359, P360, P361, P362, P363, P364, P365, P368, P369, P370, P371, P372, P373, P374, P375, P378, P379, P38, P390, P391, P392, P393, P394, P398, P399

Table 19: Number and percentage of 5484 children hospitalised one of more times in their first five years of life, and number of hospitalisations for infectious and non-infectious diseases, by type of infection.

Reason for hospitalisation	**Children, n (%)**	**Hospitalisations, n (%)**
Total hospitalisations for any cause	2492 (45.4)	5070 (100)
Hospitalisation for any infectious disease	1401(25.6)	2221 (43.8)
Respiratory infections [a]	816 (14.9)	1219 (24.0)
Gastrointestinal / intra-abdominal infections	296 (6.2)	340 (6.7)
Skin and soft tissue infections	115 (2.4)	132 (2.6)
Genitourinary infections	57 (1.1)	61 (1.2)
Other infection types	410 (7.5)	469 (9.3)
Hospitalisation for any non-infectious disease	1693 (30.9)	2849 (56.2)

Table 1 footnote: [a] Respiratory infections includes ear, nose and throat, and dental infections. Table cells with less than 10 cohort participants have been marked as "<10" to maintain participant privacy.

Table 20: Number of hospitalisations for the most frequently occurring (>10 hospitalisations) diagnostic codes, by infectious disease subcategory.

ICD–10–AM code	n.	%	Disease / condition
Respiratory infections, including ear, nose and throat, and dental infections (n=1219 hospitalisations)			
J219	281	23.1	Acute bronchiolitis, unspecified
J069	205	16.8	Acute upper respiratory infection, unspecified
J189	102	8.4	Pneumonia, unspecified
J210	88	7.2	Acute bronchiolitis due to respiratory syncytial virus
J050	75	6.2	Acute obstructive laryngitis (croup)
H669	74	6.1	Otitis media, unspecified
J22	73	6.0	Unspecified acute lower respiratory infection
J180	71	5.8	Bronchopneumonia, unspecified
J039	51	4.2	Acute tonsillitis, unspecified
J218	37	3.0	Acute bronchiolitis due to other specified organisms
J121	18	1.5	Respiratory syncytial virus pneumonia
J47	18	1.5	Bronchiectasis
K047	15	1.2	Periapical abscess without sinus
J029	13	1.1	Acute pharyngitis, unspecified
Intra–abdominal and gastrointestinal infections (n=340 hospitalisations)			
A099	196	57.7	Gastroenteritis and colitis of unspecified origin
A080	52	15.3	Rotaviral enteritis
A084	49	14.4	Viral intestinal infection, unspecified
A090	16	4.7	Other and unspecified gastroenteritis and colitis of infectious origin
Skin and soft tissue infections (n=132 hospitalisations)			
L0311	27	20.2	Cellulitis of other parts of limb
L024	16	11.9	Cutaneous abscess, furuncle and carbuncle of limb
L040	10	7.5	Acute lymphadenitis of face, head and neck
Genitourinary infections (n=61 hospitalisations)			
N390	59	96.7	Urinary tract infection, site not specified
Other infection types (n=469 hospitalisations)			
B349	268	57.14	Viral infection, unspecified
R509	45	9.59	Fever, unspecified
R560	41	8.74	Febrile convulsions
B019	15	3.20	Varicella without complication
I889	10	2.13	Nonspecific lymphadenitis, unspecified

Table 21: Unadjusted and multivariable log-binomial regression-adjusted associations between explanatory variables and reduced access to healthcare

	Reduced access to healthcare		**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
Explanatory variable (n (%))	**Yes, n (%)**	**No, n (%)**		
Total cohort (n = 5484 (100))	718 (13.1)	4766 (86.9)		
Child primary ethnicity				
European / other (n = 3251 (59.3))	309 (9.5)	2942 (90.5)	Reference	Reference
Māori (n = 824 (20.2))	198 (24.0)	626 (76.0)	2.53 (2.15 – 2.97)	1.56 (1.30 – 1.86)
Pacific (n = 727 (18.3))	153 (21.1)	574 (79.0)	2.21 (1.86 – 2.64)	1.30 (1.06 – 1.59)
Asian (n = 682 (17.3))	58 (8.5)	624 (91.5)	0.89 (0.68 – 1.17)	0.88 (0.66 – 1.14)
Sex				
Female (n = 2654 (48.4))	327 (12.3)	2327 (87.7)	Reference	Reference
Male (n = 2830 (51.6))	391 (13.8)	2439 (86.2)	1.12 (0.98 – 1.29)	1.12 (0.98 – 1.27)
Maternal age in years				
≥25 (n = 4550 (83.0))	524 (11.5)	4026 (88.5)	Reference	Reference
<25 (n = 934 (17.0))	194 (20.8)	740 (79.2)	1.80 (1.55 – 2.09)	1.03 (0.88 – 1.21)
Maternal education				
Diploma or degree (n = 3935 (71.8))	427 (10.9)	3508 (89.2)	Reference	Reference
High school or below (n = 1549 (28.3))	291 (18.8)	1258 (81.2)	1.73 (1.51 – 1.99)	1.13 (0.98 – 1.31)
Gestation in weeks				
≥37 (n = 5133 (93.6))	675 (13.2)	4458 (86.9)	Reference	
<37 (n = 351 (6.4))	43 (12.3)	308 (87.8)	0.93 (0.70 – 1.24)	Excluded

Table 21 continued	**Reduced access to healthcare**		**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
Explanatory variable (n (%))	**Yes, n (%)**	**No, n (%)**		
Birthweight (full term infants only)				
≥2500 grams (n = 5401 (98.5))	710 (13.2)	4691 (86.9)	Reference	
<2500 grams (n = 83 (1.5))	<10 (9.6)	75 (90.4)	0.73 (0.38 – 1.42)	Excluded
Mode of delivery				
Vaginal (n = 4140 (75.5))	565 (13.7)	3575 (86.4)	Reference	Reference
Caesarean (n = 1344 (24.5))	153 (11.4)	1191 (88.6)	0.83 (0.71 – 0.99)	0.97 (0.82 – 1.13)
Total breast feeding duration				
≥6 months (n = 3639 (66.4))	416 (11.4)	3223 (88.6)	Reference	Reference
<6 months (n = 1845 (33.6))	302 (16.4)	1543 (83.6)	1.43 (1.25 – 1.64)	1.18 (1.03 – 1.35)
Completed first six scheduled immunisations				
Yes (n = 4910 (89.5))	619 (12.6)	4291 (87.4)	Reference	
No (n = 574 (10.5))	99 (17.3)	475 (82.8)	1.37 (1.13 – 1.66)	Excluded [a]
Completed first six scheduled immunisations within 30 days of due date				
Yes (n = 3862 (71.8))	464 (11.7)	3505 (88.3)	Reference	Reference
No (n = 1515 (28.2))	254 (16.8)	1261 (83.2)	1.43 (1.25 – 1.65)	1.14 (1.01 – 1.28)
Household deprivation (NZiDep ≥3) – at any interview [b]				
No (n = 3289 (60.0))	238 (7.2)	3051 (92.8)	Reference	Reference
Yes (n = 2195 (40.0))	480 (21.9)	1715 (78.1)	3.02 (2.61 – 3.50)	2.23 (1.89 – 2.62)

Table 21 continued	**Reduced access to healthcare**		**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
Explanatory variable (n (%))	**Yes, n (%)**	**No, n (%)**		
Lack of household heating at 9 months				
No (n = 4940 (90.1))	618 (12.5)	4322 (87.5)	Reference	Reference
Yes (n = 544 (9.9))	100 (18.4)	444 (81.6)	1.47 (1.21 – 1.78)	0.91 (0.74 – 1.10)
Use of gas heating in child's bedroom at 9 months				
No (n = 5288 (96.4))	700 (13.2)	4588 (86.8)	Reference	Reference
Yes (n = 196 (3.6))	18 (9.2)	178 (90.8)	0.69 (0.44 – 1.08)	0.69 (0.43 – 1.03)
Household smoking – at any interview				
No (n = 3541 (64.6))	338 (9.6)	3203 (90.5)	Reference	Reference
Yes (n = 1943 (35.4))	380 (19.6)	1563 (80.4)	2.05 (1.79 – 2.35)	1.22 (1.05 – 1.43)
Household crowding – at any interview				
No (n = 3881 (70.8))	406 (10.5)	3475 (89.5)	Reference	Reference
Yes (n = 1603 (29.2))	312 (19.5)	1291 (80.5)	1.86 (1.62 – 2.13)	1.14 (0.98 – 1.33)
Household rural residence – at any interview				
No (n = 4864 (88.7))	635 (13.1)	4229 (86.9)	Reference	
Yes (n = 620 (11.3))	83 (13.4)	537 (86.6)	1.03 (0.83 – 1.27)	Excluded
Moved house ≥4 times prior to age 5				
No (n = 4882 (89.0))	602 (12.3)	4280 (87.7)	Reference	Reference
Yes (n = 602 (11.0))	116 (19.3)	486 (80.7)	1.56 (1.31 – 1.87)	1.01 (0.85 – 1.22)
Maternal experience of racism in healthcare – at any interview				
No (n = 5148 (93.9))	627 (12.2)	4521 (87.8)	Reference	Reference
Yes (n = 336 (6.1))	91 (27.1)	245 (72.9)	2.22 (1.84 – 2.69)	1.59 (1.32 – 1.89)

Table 21 footnote: Table cells with less than 10 cohort participants have been marked as "<10" to maintain participant privacy. 'Excluded' = excluded from multivariable model due to unadjusted P–value ≥0.15. [a] Immunisation completeness was excluded from the multivariable model due to correlation with delayed immunisation. [b] NZiDep is an 5–point scale measuring individual financial deprivation derived from 8 questions regarding employment status, receipt of government benefits or charity, and the need to save money on food, heating, or footwear.

Table 22: Reasons for lack of access to healthcare

Reason for lack of access to healthcare	Data collection wave (child age)		
	9 months, n	**2 years, n**	**4½ years, n**
Difficulty paying for medical care or medicines	174	13	<10
Did not collect prescription due to cost	157		
Had no transport		38	15
Lack of childcare		<10	<10
Couldn't obtain appointment soon enough / at a suitable time		132	147
It was after hours		60	67
Couldn't get in touch with doctor		<10	<10
Couldn't spare the time		16	12

Table 22 footnote: In NZ, attendance at the general practice with which the child is registered has been fully funded since 1996, so was free to the children in this study throughout the study period. However, during the study period after-hours care would still have attracted a fee. Zero-fees access was extended to children under 13 and to after-hours care in 2015, after the end of data collection for this study.

Table 23: Unadjusted and multivariable log-binomial regression-adjusted associations between explanatory variables and hospitalisation for an infectious disease (ID) in the first five years of life

Explanatory variable (n (%))	**Hospitalised for an ID**		**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) – with ethnicity**	**Adjusted RR (95% CI) – without ethnicity**
	Yes, n (%)	**No, n (%)**			
Total cohort (n = 5484 (100))	1401 (25.6)	4083 (74.5)			
Child primary ethnicity					
European/Other (n = 3251 (59.3))	650 (20.0)	2601 (80.0)	Reference	Reference	Excluded
Māori (n = 824 (20.2))	278 (33.7)	546 (66.3)	1.69 (1.50 – 1.90)	1.35 (1.18 – 1.53)	Excluded
Pacific (n = 727 (18.3))	308 (42.4)	419 (57.6)	2.12 (1.90 – 2.36)	1.56 (1.36 – 1.79)	Excluded
Asian (n = 682 (17.3))	165 (24.2)	517 (75.8)	1.21 (1.04 – 1.41)	1.12 (0.95 – 1.30)	Excluded
Sex					
Female (n = 2654 (48.4))	611 (23.0)	2043 (77.0)	Reference	Reference	Reference
Male (n = 2830 (51.6))	790 (27.9)	2040 (72.1)	1.21 (1.11 – 1.33)	1.19 (1.09 – 1.29)	1.18 (1.08 – 1.29)
Maternal age					
≥25 years (n = 4550 (83.0))	1052 (23.1)	3498 (76.9)	Reference	Reference	Reference
<25 years (n = 934 (17.0))	349 (37.4)	585 (62.6)	1.62 (1.46 – 1.78)	1.28 (1.15 – 1.42)	1.31 (1.17 – 1.46)
Maternal education					
Diploma or degree (n = 3935 (71.8))	914 (23.2)	3021 (76.8)	Reference	Reference	Reference
High school or below (n = 1549 (28.3))	487 (31.4)	1062 (68.6)	1.35 (1.23 – 1.49)	1.02 (0.95 – 1.12)	1.05 (0.96 – 1.16)

Table 23 continued	**Hospitalised for an ID**		**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) – with ethnicity**	**Adjusted RR (95% CI) – without ethnicity**
Explanatory variable (n (%))	**Yes – n (%)**	**No – n (%)**			
Gestation					
≥37 weeks (n = 5133 (93.6))	1288 (25.1)	3845 (74.9)	Reference	Reference	Reference
<37 weeks (n = 351 (6.4))	113 (32.2)	238 (67.8)	1.28 (1.09 – 1.50)	1.26 (1.07 – 1.35)	1.25 (1.06 – 1.43)
Birthweight (full term infants only)					
≥2500 grams (n = 5401 (98.5))	1373 (25.4)	4028 (74.6)	Reference	Reference	Reference
<2500 grams (n = 83 (1.5))	28 (33.7)	55 (66.3)	1.33 (0.98 – 1.80)	1.38 (0.99 – 1.53)	1.37 (0.99 – 1.63)
Mode of delivery					
Vaginal (n = 4140 (75.5))	1042 (25.2)	3098 (74.8)	Reference		
Caesarean (n = 1344 (24.5))	359 (26.7)	985 (73.3)	1.06 (0.96 – 1.18)	Excluded	Excluded
Total breast feeding duration					
≥6 months (n = 3639 (66.4))	840 (23.1)	2799 (76.9)	Reference	Reference	Reference
<6 months (n = 1845 (33.6))	561 (30.4)	1284 (69.6)	1.32 (1.20 – 1.44)	1.18 (1.08 – 1.29)	1.18 (1.08 – 1.30)
Completed first six scheduled immunisations					
Yes (n = 4910 (89.5))	1256 (25.6)	3654 (74.4)	Reference		
No (n = 574 (10.5))	145 (25.3)	429 (74.7)	0.99 (0.85 – 1.15)	Excluded	Excluded
Completed first six scheduled immunisations within 30 days of due date					
Yes (n = 3862 (71.8))	983 (24.8)	2986 (75.2)	Reference	Reference	Reference
No (n = 1515 (28.2))	418 (27.6)	1097 (72.4)	1.11 (1.01 – 1.23)	1.02 (0.94 – 1.11)	1.04 (0.95 – 1.13)

Table 23 continued	**Hospitalised for an ID**		**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) – with ethnicity**	**Adjusted RR (95% CI) – without ethnicity**
Explanatory variable (n (%))	**Yes – n (%)**	**No – n (%)**			
Household deprivation (NZiDep ≥3) – at any interview [a]					
No (n = 3289 (60.0))	674 (20.5)	2615 (79.5)	Reference	Reference	Reference
Yes (n = 2195 (40.0))	727 (33.1)	1468 (66.9)	1.62 (1.48 – 1.77)	1.24 (1.12 – 1.37)	1.29 (1.17 – 1.43)
Lack of household heating at 9 months					
No (n = 4940 (90.1))	1187 (24.0)	3753 (76.0)	Reference	Reference	Reference
Yes (n = 544 (9.9))	214 (39.3)	330 (60.7)	1.64 (1.46 – 1.84)	1.20 (1.06 – 1.33)	1.32 (1.17 – 1.48)
Use of gas heating in child's bedroom at 9 months					
No (n = 5288 (96.4))	1339 (25.3)	3949 (74.7)	Reference	Reference	Reference
Yes (n = 196 (3.6))	62 (31.6)	134 (68.37)	1.25 (1.01 – 1.54)	1.35 (1.08 – 1.63)	1.34 (1.07 – 1.63)
Household smoking – at any interview					
No (n = 3541 (64.6))	798 (22.5)	2743 (77.5)	Reference	Reference	Reference
Yes (n = 1943 (35.4))	603 (31.0)	1340 (69.0)	1.38 (1.26 – 1.51)	0.96 (0.87 – 1.06)	1.01 (0.91 – 1.11)
Household crowding – at any interview					
No (n = 3881 (70.8))	852 (22.0)	3029 (78.1)	Reference	Reference	Reference
Yes (n = 1603 (29.2))	549 (34.3)	1054 (65.8)	1.56 (1.43 – 1.71)	1.08 (0.97 – 1.20)	1.21 (1.09 – 1.33)
Household rural residence – at any interview					
No (n = 4864 (88.7))	1284 (26.4)	3580 (73.6)	Reference	Reference	Reference
Yes (n = 620 (11.3))	117 (18.9)	503 (81.1)	0.71 (0.60 – 0.85)	0.82 (0.69 – 0.97)	0.76 (0.64 – 0.89)

Table 23 continued	**Hospitalised for an ID**		**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) – with ethnicity**	**Adjusted RR (95% CI) – without ethnicity**
Explanatory variable (n (%))	**Yes – n (%)**	**No – n (%)**			
Moved house ≥4 times prior to age 5					
No (n = 4882 (89.0))	1219 (25.0)	3663 (75.0)	Reference	Reference	Reference
Yes (n = 602 (11.0))	182 (30.2)	420 (69.8)	1.21 (1.06 – 1.38)	0.97 (0.85 – 1.10)	0.95 (0.83 – 1.07)
Reduced healthcare access – at any interview					
No (n = 4766 (86.9))	1153 (24.2)	3613 (75.8)	Reference	Reference	Reference
Yes (n = 718 (13.1))	248 (34.5)	470 (65.5)	1.43 (1.28 – 1.60)	1.13 (1.01 – 1.24)	1.15 (1.03 – 1.29)
Maternal experience of racism in healthcare – at any interview					
No (n = 5148 (93.9))	1282 (24.9)	3866 (75.1)	Reference	Reference	Reference
Yes (n = 336 (6.1))	119 (35.4)	217 (64.6)	1.42 (1.22 – 1.66)	1.16 (1.00 – 1.33)	1.20 (1.03 – 1.38)

Table 23 footnote: 'Excluded' = excluded from baseline model due to unadjusted P–value ≥0.15. [a] NZiDep is an 5–point scale measuring individual financial deprivation derived from 8 questions regarding employment status, receipt of government benefits or charity, and the need to save money on food, heating, or footwear.

Table 24: Unadjusted and multivariable log-binomial regression-adjusted associations between explanatory variables and hospitalisation for an infectious disease (ID) in the first five years of life, using total-response ethnicity. Ethnic groups thus overlap and are treated as independent so cannot be directly compared.

Explanatory variable (n (%))	**Hospitalised for an ID**		**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
	Yes, n (%)	**No, n (%)**		
Total cohort (n = 5484 (100))	1401 (25.6)	4083 (74.5)		
Ethnicity				
Total-response European/Other ethnicity (n = 4253 (77.6))	959 (22.6)	3294 (77.5)	0.63 (0.57 – 0.69)	0.82 (0.73 – 0.93)
Total-response Māori ethnicity (n = 1336 (24.4))	410 (30.7)	926 (69.3)	1.28 (1.17 – 1.42)	1.09 (0.99 – 1.21)
Total–response Pacific ethnicity (n = 1059 (19.3))	417 (39.4)	642 (60.6)	1.77 (1.61 – 1.94)	1.24 (1.09 – 1.40)
Total–response Asian ethnicity (n = 805 (14.7))	203 (25.2)	602 (74.8)	0.98 (0.87 – 1.12)	0.97 (0.83 – 1.12)
Male gender (n = 2830 (51.6))	790 (27.9)	2040 (72.1)	1.21 (1.11 – 1.33)	1.18 (1.08 – 1.29)
Maternal age <25 years (n = 934 (17.0))	349 (37.4)	585 (62.6)	1.62 (1.46 – 1.78)	1.28 (1.15 – 1.42)
Maternal education high school or below (n = 1549 (28.3))	487 (31.4)	1062 (68.6)	1.35 (1.23 – 1.49)	1.02 (0.93 – 1.13)
Gestation <37 weeks (n = 351 (6.4))	113 (32.2)	238 (67.8)	1.28 (1.09 – 1.50)	1.26 (1.08 – 1.38)
Birthweight <2500 g at term (n = 83 (1.5))	28 (33.7)	55 (66.3)	1.33 (0.98 – 1.80)	1.38 (1.00 – 1.77)
Caesarean mode of delivery (n = 1344 (24.5))	359 (26.7)	985 (73.3)	1.06 (0.96 – 1.18)	Excluded
Total breastfeeding duration <6 months (n = 1845 (33.6))	561 (30.4)	1284 (69.6)	1.32 (1.20 – 1.44)	1.17 (1.07 – 1.28)
Incomplete immunisations [a] (n = 574 (10.5))	145 (25.3)	429 (74.7)	0.99 (0.85 – 1.15)	Excluded
Delayed immunisations [b] (n = 1515 (28.2))	418 (27.6)	1097 (72.4)	1.11 (1.01 – 1.23)	1.03 (0.94 – 1.11)
Household deprivation [c] (n = 2195 (40.0))	727 (33.1)	1468 (66.9)	1.62 (1.48 – 1.77)	1.25 (1.13 – 1.38)
Lack of household heating [d] (n = 544 (9.9))	214 (39.3)	330 (60.7)	1.64 (1.46 – 1.84)	1.20 (1.06 – 1.35)
Gas heating in child's room [d] (n = 196 (3.6))	62 (31.6)	134 (68.37)	1.25 (1.01 – 1.54)	1.32 (1.06 – 1.60)

Table 24 continued	**Hospitalised for an ID**		**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
Explanatory variable (n (%))	**Yes, n (%)**	**No, n (%)**		
Household smoking [e] (n = 1943 (35.4))	603 (31.0)	1340 (69.0)	1.38 (1.26 – 1.51)	0.96 (0.87 – 1.06)
Household crowding [e] (n = 1603 (29.2))	549 (34.3)	1054 (65.8)	1.56 (1.43 – 1.71)	1.08 (0.97 – 1.21)
Household rural residence [e] (n = 620 (11.3))	117 (18.9)	503 (81.1)	0.71 (0.60 – 0.85)	0.81 (0.68 – 0.95)
Moved house ≥4 times prior to age 5 (n=602 (11.0))	182 (30.2)	420 (69.8)	1.21 (1.06 – 1.38)	0.98 (0.86 – 1.12)
Reduced healthcare access [e] (n = 718 (13.1))	248 (34.5)	470 (65.5)	1.43 (1.28 – 1.60)	1.14 (1.01 – 1.27)
Maternal experience of racism in healthcare [e] (n = 336 (6.1))	119 (35.4)	217 (64.6)	1.42 (1.22 – 1.66)	1.19 (1.03 – 1.37)

Table 24 footnote: 'Excluded' = excluded from baseline model due to unadjusted P–value ≥0.15. [a] In the first year of life. [b] In the first year of life, not completed within 30 days of due date. [c] NZiDep ≥3 at any interview. [d] At 9 month interview. [e] At any interview

Table 25: Unadjusted and multivariable Poisson regression-adjusted associations between explanatory variables and hospitalisation for an infectious disease (ID) in the first five years of life, within the subgroup of 3251 cohort children prioritised to European/Other ethnic group.

Explanatory variable	**Exposed**	**Hospitalised for an ID**		**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
		Yes, n (%)	**No, n (%)**		
Total	3251 (100)	650 (20.0)	2601 (80.0)		
Male gender	1656 (50.9)	361 (21.8)	1295 (78.2)	1.20 (1.05 – 1.38)	1.21 (1.05 – 1.39)
Maternal age <25 years	352 (10.8)	110 (31.3)	242 (68.8)	1.68 (1.41 – 1.99)	1.48 (1.19 – 1.82)
Lower maternal education	693 (21.3)	160 (23.1)	533 (76.9)	1.21 (1.03 – 1.41)	1.03 (0.87 – 1.22)
Gestation <37 weeks	222 (6.8)	58 (26.1)	164 (73.9)	1.34 (1.06 – 1.69)	1.24 (0.96 – 1.57)
Birthweight <2500 g at term	40 (1.2)	16 (40.0)	24 (60.0)	2.03 (1.38 – 2.98)	2.09 (1.29 – 3.17)
Caesarean mode of delivery	866 (26.6)	192 (22.2)	674 (77.8)	1.15 (0.99 – 1.33)	1.13 (0.97 – 1.32)
Total breastfeeding <6 months	1008 (31.0)	252 (25.0)	756 (75.0)	1.41 (1.23 – 1.62)	1.26 (1.09 – 1.46)
Incomplete immunisations [a]	351 (10.8)	71 (20.2)	280 (79.8)	1.01 (0.81 – 1.26)	Excluded
Delayed immunisations [b]	858 (26.4)	183 (21.3)	675 (78.7)	1.09 (0.94 – 1.27)	Excluded
Household deprivation [c]	998 (30.7)	260 (26.1)	738 (74.0)	1.51 (1.31 – 1.73)	1.32 (1.13 – 1.55)
Lack of household heating [d]	118 (3.6)	21 (17.8)	97 (82.2)	0.89 (0.60 – 1.31)	Excluded
Gas heating in child's room [d]	130 (4.0)	39 (30.0)	91 (70.0)	1.53 (1.17 – 2.01)	1.49 (1.10 – 1.98)
Household smoking [e]	784 (24.1)	176 (22.5)	608 (77.6)	1.17 (1.00 – 1.36)	0.88 (0.74 – 1.05)
Household crowding [e]	438 (13.5)	110 (25.1)	328 (74.9)	1.31 (1.09 – 1.56)	1.13 (0.93 – 1.36)
Household rural residence [e]	517 (15.9)	83 (16.1)	434 (84.0)	0.77 (0.63 – 0.96)	0.74 (0.60 – 0.91)
Moved house ≥4 times [f]	289 (8.9)	69 (23.9)	220 (76.1)	1.22 (0.98 – 1.51)	0.98 (0.77 – 1.23)
Reduced healthcare access [e]	309 (9.5)	88 (28.5)	221 (71.5)	1.49 (1.23 – 1.81)	1.32 (1.07 – 1.62)
Racism in healthcare [e]	120 (3.7)	29 (24.2)	91 (75.8)	1.22 (0.88 – 1.69)	Excluded

Table 25 footnote: 'Excluded' = excluded from baseline model due to unadjusted P–value ≥0.15. [a] In the first year of life. [b] In the first year of life, not completed within 30 days of due date. [c] NZiDep ≥3 at any interview. [d] At 9 month interview. [e] At any interview. [f] prior to 5 years of age.

Table 26: Unadjusted and multivariable log-binomial regression-adjusted associations between explanatory variables and hospitalisation for an infectious disease (ID) in the first five years of life, within the subgroup of 824 cohort children prioritised to Māori ethnic group

Explanatory variable	**Exposed**	**Hospitalised for an ID**		**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)** [a]
		Yes, n (%)	**No, n (%)**		
Total	824 (100)	278 (33.7)	546 (66.3)		
Male gender	437 (53.0)	163 (37.3)	274 (62.7)	1.26 (1.03 – 1.53)	1.30 (1.07 – 1.58)
Maternal age <25 years	279 (33.9)	113 (40.5)	166 (59.5)	1.34 (1.11 – 1.62)	1.27 (1.03 – 1.56)
Lower maternal education	352 (42.7)	132 (37.5)	220 (62.5)	1.21 (1.00 – 1.47)	1.09 (0.90 – 1.33)
Gestation <37 weeks	48 (5.8)	22 (45.8)	26 (54.2)	1.39 (1.01 – 1.92)	1.22 (0.85 – 1.63)
Birthweight <2500 g at term	12 (1.5)	<10 (16.7)	10 (83.3)	0.49 (0.14 – 1.74)	Excluded
Caesarean mode of delivery	154 (18.7)	60 (39.0)	94 (61.0)	1.20 (0.96 – 1.50)	1.24 (0.98 – 1.53)
Total breastfeeding <6 months	324 (39.3)	113 (34.9)	211 (65.1)	1.06 (0.87 – 1.28)	Excluded
Incomplete immunisations [a]	120 (14.6)	32 (26.7)	88 (73.3)	0.76 (0.56 – 1.04)	0.90 (0.69 – 1.13)
Delayed immunisations [b]	321 (39.0)	106 (33.0)	215 (67.0)	0.97 (0.79 – 1.18)	Excluded
Household deprivation [c]	501 (60.8)	182 (36.3)	319 (63.7)	1.22 (1.00 – 1.50)	1.05 (0.85 – 1.31)
Lack of household heating [d]	85 (10.3)	38 (44.7)	47 (55.3)	1.38 (1.06 – 1.78)	1.31 (0.99 – 1.66)
Gas heating in child's room [d]	35 (4.3)	13 (37.1)	22 (62.9)	1.11 (0.71 – 1.72)	Excluded
Household smoking [e]	502 (60.9)	183 (36.5)	319 (63.6)	1.24 (1.01 – 1.52)	1.11 (0.90 – 1.39)
Household crowding [e]	358 (43.5)	129 (36.0)	229 (64.0)	1.13 (0.93 – 1.36)	Excluded
Household rural residence [e]	92 (11.2)	28 (30.4)	64 (69.6)	0.89 (0.64 – 1.23)	Excluded
Moved house ≥4 times [f]	174 (21.1)	63 (36.2)	111 (63.8)	1.09 (0.87 – 1.37)	Excluded
Reduced healthcare access [e]	198 (24.0)	74 (37.4)	124 (62.6)	1.15 (0.93 – 1.42)	Excluded
Racism in healthcare [e]	101 (12.3)	46 (45.5)	55 (54.5)	1.42 (1.12 – 1.80)	1.41 (1.10 – 1.76)

Table 26 footnote: 'Excluded' = excluded from baseline model due to unadjusted P–value ≥0.15. [a] In the first year of life. [b] In the first year of life, not completed within 30 days of due date. [c] NZiDep ≥3 at any interview. [d] At 9 month interview. [e] At any interview. [f] prior to 5 years of age.

Table 27: Unadjusted and multivariable log-binomial regression-adjusted associations between explanatory variables and hospitalisation for an infectious disease (ID) in the first five years of life, within the subgroup of 727 cohort children prioritised to Pacific ethnic group

Explanatory variable	**Exposed**	**Hospitalised for an ID**		**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)** [a]
		Yes, n (%)	**No, n (%)**		
Total	727 (100)	308 (42.4)	419 (57.6)		
Male gender	383 (52.7)	172 (44.9)	211 (55.1)	1.14 (0.96 – 1.35)	1.13 (0.96 – 1.34)
Maternal age <25 years	233 (32.1)	112 (48.1)	121 (51.9)	1.21 (1.02 – 1.44)	1.20 (1.01 – 1.41)
Lower maternal education	369 (50.8)	162 (43.9)	207 (56.1)	1.08 (0.91 – 1.28)	Excluded
Gestation <37 weeks	43 (5.9)	20 (46.5)	23 (53.5)	1.10 (0.79 – 1.54)	Excluded
Birthweight <2500 g at term	<10 (0.8)	<10 (50.0)	<10 (50.0)	1.18 (0.53 – 2.64)	Excluded
Caesarean mode of delivery	131 (18.0)	51 (38.9)	80 (61.1)	0.90 (0.71 – 1.14)	Excluded
Total breastfeeding <6 months	296 (40.7)	142 (48.0)	154 (52.0)	1.25 (1.05 – 1.47)	1.24 (1.05 – 1.46)
Incomplete immunisations [a]	70 (9.6)	33 (47.1)	37 (52.9)	1.13 (0.87 – 1.47)	Excluded
Delayed immunisations [b]	239 (32.9)	105 (43.9)	134 (56.1)	1.06 (0.88 – 1.26)	Excluded
Household deprivation [c]	508 (69.9)	233 (45.9)	275 (54.1)	1.34 (1.09 – 1.65)	1.28 (1.04 – 1.59)
Lack of household heating [d]	260 (35.8)	130 (50.0)	130 (50.0)	1.31 (1.11 – 1.55)	1.28 (1.08 – 1.51)
Gas heating in child's room [d]	14 (1.9)	<10 (50.0)	<10 (50.0)	1.18 (0.70 – 2.01)	Excluded
Household smoking [e]	459 (63.1)	198 (43.1)	261 (56.9)	1.05 (0.88 – 1.26)	Excluded
Household crowding [e]	514 (70.7)	228 (44.4)	286 (55.6)	1.18 (0.97 – 1.44)	1.04 (0.86 – 1.28)
Household rural residence [e]	<10 (1.2)	<10 (55.6)	<10 (44.4)	1.32 (0.73 – 2.38)	Excluded
Moved house ≥4 times [f]	91 (12.5)	46 (50.6)	45 (49.5)	1.23 (0.98 – 1.53)	1.16 (0.92 – 1.42)
Reduced healthcare access [e]	153 (21.1)	72 (47.1)	81 (52.9)	1.14 (0.94 – 1.39)	Excluded
Racism in healthcare [e]	72 (9.9)	32 (44.4)	40 (55.6)	1.05 (0.80 – 1.39)	Excluded

Table 25 footnote: 'Excluded' = excluded from baseline model due to unadjusted P–value ≥0.15. [a] In the first year of life. [b] In the first year of life, not completed within 30 days of due date. [c] NZiDep ≥3 at any interview. [d] At 9 month interview. [e] At any interview. [f] prior to 5 years of age.

Table 28: Unadjusted and multivariable log-binomial regression-adjusted associations between explanatory variables and hospitalisation for an infectious disease (ID) in the first five years of life, within the subgroup of 682 cohort children prioritised to Asian ethnic group

Explanatory variable	**Exposed**	**Hospitalised for an ID**		**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)** [a]
		Yes, n (%)	**No, n (%)**		
Total	682 (100)	165 (24.2)	517 (75.8)		
Male gender	354 (51.9)	94 (26.6)	260 (73.5)	1.23 (0.94 – 1.61)	1.2 (0.92 – 1.57)
Maternal age <25 years	70 (10.3)	14 (20.0)	56 (80.0)	0.81 (0.50 – 1.32)	Excluded
Lower maternal education	135 (19.8)	33 (24.4)	102 (75.6)	1.01 (0.73 – 1.41)	Excluded
Gestation <37 weeks	38 (5.6)	13 (34.2)	25 (65.8)	1.45 (0.91 – 2.30)	1.43 (0.84 – 2.18)
Birthweight <2500 g at term	25 (3.7)	<10 (28.0)	18 (72.0)	1.16 (0.61 – 2.22)	Excluded
Caesarean mode of delivery	193 (28.3)	56 (29.0)	137 (71.0)	1.30 (0.99 – 1.72)	1.18 (0.88 – 1.55)
Total breastfeeding <6 months	217 (31.8)	54 (24.9)	163 (75.1)	1.04 (0.79 – 1.38)	Excluded
Incomplete immunisations [a]	33 (4.8)	<10 (27.3)	24 (72.7)	1.13 (0.64 – 2.01)	Excluded
Delayed immunisations [b]	97 (14.2)	24 (24.7)	73 (75.3)	1.03 (0.71 – 1.49)	Excluded
Household deprivation [c]	188 (27.6)	52 (27.7)	136 (72.3)	1.21 (0.91 – 1.60)	1.19 (0.89 – 1.56)
Lack of household heating [d]	81 (11.9)	25 (30.9)	56 (69.1)	1.33 (0.93 – 1.89)	1.31 (0.89 – 1.83)
Gas heating in child's room [d]	17 (2.5)	<10 (17.7)	14 (82.4)	0.72 (0.26 – 2.04)	Excluded
Household smoking [e]	198 (29.0)	46 (23.2)	152 (76.8)	0.94 (0.70 – 1.27)	Excluded
Household crowding [e]	293 (43.0)	82 (28.0)	211 (72.0)	1.31 (1.01 – 1.71)	1.26 (0.97 – 1.65)
Household rural residence [e]	<10 (0.3)	<10 (50.0)	<10 (50.0)	2.07 (0.52 – 8.34)	Excluded
Moved house ≥4 times [f]	48 (7.0)	<10 (8.3)	44 (91.7)	0.33 (0.13 – 0.85)	0.31 (0.10 – 0.70)
Reduced healthcare access [e]	58 (8.5)	14 (24.1)	44 (75.9)	1.00 (0.62 – 1.61)	Excluded
Racism in healthcare [e]	43 (6.3)	12 (27.9)	31 (72.1)	1.17 (0.71 – 1.92)	Excluded

Table 25 footnote: 'Excluded' = excluded from baseline model due to unadjusted P–value ≥0.15. [a] In the first year of life. [b] In the first year of life, not completed within 30 days of due date. [c] NZiDep ≥3 at any interview. [d] At 9 month interview. [e] At any interview. [f] prior to 5 years of age.

CHAPTER 7: *STAPHYLOCOCCUS AUREUS* COLONISATION AND RISK OF SKIN AND SOFT TISSUE INFECTION IN NEW ZEALAND CHILDREN

Chapter 6 demonstrated that just over a quarter of the cohort experienced one or more hospitalisations for an ID, with respiratory and gastrointestinal infections being the most common infections leading to hospitalisation. In this context, skin and soft tissue infections (SSTI) were relatively less common but were still an important cause of hospitalisation. However hospitalisation data identifies only a small proportion of SSTI; research conducted in the Tairawhiti region of NZ showed that there were 14 cases of SSTI managed in primary care for each case managed in the hospital (21).

This chapter looks at SSTI in more detail, including both SSTI managed in hospital and SSTI reported by parents and managed in the community. The range of pathogens which commonly cause SSTI is narrow; *Staphylococcus aureus*, *Streptococcus pyogenes* (Lancefield group A streptococcus) and other β-haemolytic streptococci (particularly from Lancefield groups C and G) cause the majority of SSTI and may be cultured from infected lesions alone or in combination. While Chapter 6 included a broad range of host and environmental covariates, this chapter includes more focused list of covariates while incorporating data on *S. aureus* colonisation obtained from swabs collected from the anterior nares, oropharynx, and antecubital fossa. An association was sought between *S. aureus* colonisation and risk of SSTI.

SSTI was found to be common, affecting 29.4% of the cohort in the first five years of life. Māori and Pacific children were more likely to have experienced an SSTI, and had a very high rate of hospitalisation for an SSTI by international comparison. Colonisation with *S. aureus* was associated with a small increase in risk of SSTI, with the relationship being stronger when restricted to SSTI outcomes in the year prior to swab collection and for colonisation of the skin. Eczema also had a strong association with an increased risk of SSTI.

The research described in this chapter has been published in the *European Journal of Clinical Microbiology & Infectious Diseases*:

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7.1 INTRODUCTION

New Zealand (NZ) children experience high rates of skin and soft tissue infection (SSTI) caused by *Staphylococcus aureus* (218). The incidence of SSTI is highest in children under 5 years of age, Māori or Pacific children, and children in the most socioeconomically deprived areas of NZ (3, 104). Recent data from NZ showed that methicillin-resistant *S. aureus* (MRSA) accounted for 8% of *S. aureus* isolates from skin infections in primary care, and isolation of MRSA was more common in people of Māori or Pacific ethnicity (22).

Asymptomatic colonisation with *S. aureus* is common, with nasal colonisation prevalence typically estimated to be in the range of 20-50% (219, 220). Other colonisation sites include the skin and gastrointestinal tract, particularly the oropharynx (221). Colonisation is dynamic; prevalence declines with age and colonising strains change over months to years (220, 222, 223). At the nasal site, individuals may be either persistently or intermittently colonised, or resistant to colonisation (224). Persistently colonised individuals harbour greater densities of *S. aureus* in the anterior nares and consequently, density can be used to identify persistent colonisation (43). Several host gene variants have been found to be associated with *S. aureus* colonisation, as have features of the nasal and skin microbiota (225-228).

S. aureus colonisation is thought to be a precursor to developing disease. Persistent, but not intermittent, colonisation has been associated with an increased risk of nosocomial *S. aureus* infection (229, 230). However, a link between colonisation and community-onset disease has not been established. In this study we aimed to use the *Growing Up in New Zealand* longitudinal birth cohort to determine the prevalence of and risk factors for *S. aureus* colonisation, and to examine whether *S. aureus* colonisation was associated with community-onset *S. aureus* infection in the form of SSTI.

7.2 METHODS

7.2.1 Study sample

This study was completed within the *Growing up in New Zealand* longitudinal birth cohort study. The study recruited 6822 pregnant mothers, and the cohort comprises their 6853 children born in 2009 and 2010, representing 11% of the national birth cohort over that period (37). The cohort is broadly generalisable to the national birth cohort with regards to ethnicity and socioeconomic status (38, 39).

7.2.2 Ethics

Primary caregivers of participating children provided written informed consent for microbiological sampling, and for linkage with administrative health datasets. Ethical approval was obtained from the Ministry of Health Northern Y Regional Ethics Committee (NTY/08106/055).

7.2.3 Data collection and measurement

Explanatory variables

Data describing each child's demographic features, maternal and perinatal characteristics, socioeconomic status, and the household environment were obtained from face-to-face interviews completed with caregivers when their child was 9 months, 2 years and 4½ years old, and from telephone interviews conducted during intervening periods.

Child ethnicity was analysed in broad categories – Māori, Pacific, Asian, and a combined comparator group of European and all other ethnicities – using the main ethnicity identified for the child by their primary caregiver.

Prematurity was defined as birth prior to 37 weeks of gestation. Low birth weight at term was defined as birth after 37 weeks gestation with a birth weight less than 2500g. The diagnosis of eczema was based on caregiver selection of the "Eczema or dermatitis" response to the

following question asked at the 4½ year interview: “Which, if any, of these common childhood illnesses has (cohort child name) had in the last 12 months?”. No prompts or education about the diagnosis of eczema were given.

Socioeconomic deprivation was measured using a validated, individualised index, the NZiDep (50). The NZiDep is scored from 1 (least deprived) to 5 (most deprived), and is derived from 8 questionnaire items regarding employment status, receipt of government benefits or charity, and the need to make compromises to save money on food, heating, or footwear. NZiDep was assessed at 9 months and at 4½ years, and deprivation defined as an NZiDep score of ≥3 at either interview. Household crowding was defined as a ratio of household occupants to bedrooms of ≥2. Rural residence was defined using the family’s residential address and assigned as classified by Statistics New Zealand. Household crowding, tobacco smoke exposure, and rural residence were assessed at three interviews (9 and 23 months, and 4½ years). Responses for these variables have been categorised into exposure at none, or at one or more of the interviews.

Microbiological sampling

Trained interviewers collected swab samples (Copan eSwab (Brescia, Italy)) from the anterior nares (“nasal”), oropharynx, and antecubital fossa skin (“skin”) of children at the 4½ year interview. Culture was performed by Labtests (Auckland, NZ). Samples were cultured for 48 hours at 35°C in 5% CO_2, with nasal and skin swabs cultured on tryptic soy sheep blood agar and oropharyngeal swabs on 3% salt Columbia sheep blood agar. Suspected colonies of *S. aureus* were identified using matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry (BD Bruker MALDI Biotyper, Becton, Dickinson and Company, Franklin Lakes, New Jersey, U.S.A). Density of growth was visually assessed by laboratory staff as “heavy”, “moderate”, or “light” density, or as <10 colonies per plate. *S. aureus* susceptibility to cefoxitin, erythromycin, and trimethoprim-sulfamethoxazole was determined by disc diffusion using Clinical and Laboratory Standards Institute (CLSI) criteria (231). Cultures of *S. aureus* resistant to cefoxitin were defined as MRSA.

Outcome variables

This study consisted of two parts, one investigating *S. aureus* colonisation and the other prevalence of SSTI. The primary outcome for the colonisation study was *S. aureus* colonisation at any density of growth and at any sampling site. Secondary outcomes for the colonisation study were nasal colonisation at a heavy density, and skin colonisation at any density. We interpreted a heavy density of nasal colonisation as being suggestive of persistent colonisation (43).

The primary outcome for the SSTI study was a composite endpoint combining hospitalisation for SSTI or caregiver-reported SSTI at any time before the age of five years. Hospitalisation for SSTI was identified using discharge diagnostic codes used in the National Minimum Dataset (NMDS), a national administrative dataset describing all public hospital admissions. All acute paediatric inpatient care in NZ is provided at public hospitals. NMDS diagnoses are coded using the Australian Modification of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10-AM) (151). SSTI diagnoses were identified using a list of codes informed by previous work by O'Sullivan and Baker (**Table 29**) (102). Caregiver-reported SSTI was based on selection of "Skin infections" as a response to the same question in the interview at 4½ years of child age as mentioned regarding eczema above, and similar questions asked in interviews at 9 months and 2 years of child age. The prompt "where the skin is red or warm or painful or swollen, or there are pustules or boils, or crusting or oozing" was provided, and caregivers were cautioned that "this does NOT include cradle cap, mild nappy rash, eczema, or dermatitis".

As *S. aureus* colonisation is dynamic (220), we did not assume that colonisation at 4½ years of age was indicative of colonisation throughout childhood. As a secondary outcome, we examined the composite SSTI outcome within the year prior to the 4½ year interview to determine whether the risk of SSTI was greater with closer proximity in time to microbiological sampling.

7.2.4 Statistical analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Unadjusted associations were presented as risk ratios with 95% confidence intervals, and χ^2 p-values. Multivariable analyses were performed using log-binomial regression and presented as adjusted risk ratios, 95% confidence intervals and p-values. Log-binomial regression was used as the primary outcomes were not rare and odds ratios from logistic regression would therefore overestimate effect sizes. The multivariable models included all variables described in the unadjusted analyses and were refined by stepwise removal of non-significant variables guided by the Akaike Information Criterion (232). Child ethnicity and socioeconomic deprivation were retained in the models for SSTI outcomes regardless of significance.

7.3 RESULTS

7.3.1 Associations between host and environmental factors and S. aureus colonisation

Analyses were restricted to 5126 children for whom complete results from interview data, NMDS linkage and culture results from one or more swabs were available. *S. aureus* was isolated from 1441/5006 (28.8%) nasal swabs, 1379/4868 (28.3%) oropharyngeal swabs, and 262/5105 (5.1%) skin swabs collected from the 5126 children. There was a weak correlation between colonisation at the three sites (**Table 30)**. Of 1441 children with positive nasal swabs, 435 (30.2%; 8.7% of the total cohort) had a heavy growth of *S. aureus*, suggestive of persistent colonisation. Of the 2225/5126 (43.4%) children who were colonised with *S. aureus* at one or more sites, 181 (8.1%; 3.5% of the total cohort) were colonised with a methicillin-resistant strain, of which 150/181 (82.9%) were susceptible to erythromycin and all were susceptible to trimethoprim-sulfamethoxazole.

In unadjusted analyses, colonisation with *S. aureus* at any site and at any density was associated with caregiver-reported eczema and with a lower level of maternal education (**Table 31**). *S. aureus* nasal colonisation at a heavy density of growth was negatively associated with Pacific or Asian ethnicity, and with household crowding (which was correlated with these ethnic groups) (**Table 32**). The negative relationship between heavy nasal

colonisation and Pacific or Asian ethnicity reflected a positive association between the comparator European/Other ethnic group and heavy nasal colonisation, with an unadjusted relative risk of 1.55 (95% CI 1.27 – 1.89, p<0.001) when compared with all non-European/Other ethnic groups combined. In contrast, colonisation of the skin at any density was associated with Māori or Pacific ethnicity, caregiver-reported eczema, socioeconomic deprivation, household smoking, household crowding, and urban residence (**Table 33**).

After adjustment using a multivariable log-binomial model (**Table 31**), *S. aureus* colonisation at any site and at any density was associated with caregiver-reported eczema and with a lower level of maternal education. Heavy nasal colonisation with *S. aureus* was associated with socioeconomic deprivation, but negatively associated with Pacific or Asian ethnicity, and with household crowding (**Table 32**). Colonisation of the skin at any density was associated with caregiver-reported eczema, Pacific ethnicity, and household crowding (**Table 33**).

7.3.2 Associations between host, environmental and bacterial factors, and skin and soft tissue infections

A total of 1509 (29.4%) cohort children were affected by SSTI during their first five years of life; 158 (3.1%) were hospitalised and 1443 (28.2%) had a caregiver-reported SSTI. In the year prior to swab collection, 629 (12.3%) were affected by SSTI, of which 33 (0.6%) were hospitalised and 611 (11.9%) had a caregiver-reported SSTI.

The 158 hospitalised children experienced a total of 180 hospitalisations over 5 years, translating to a rate of 702 hospitalisations per 100,000 children per year. Hospitalisation for SSTI during the first five years of life affected 26/613 Māori children (4.2%, 27 hospitalisations, 881/100,000/year), 59/722 Pacific children (8.2%, 69 hospitalisations, 1911/100,000/year), and 10/591 Asian children (1.7%, 12 hospitalisations, 406/100,000/year), compared with 63/3200 European/Other children (2.0%, 72 hospitalisations, 450/100,000/year).

In unadjusted analyses (**Table 34**), SSTI in the first five years of life was associated with *S. aureus* colonisation at any site and at any density, and with colonisation of the skin at any density, but not with heavy nasal colonisation. SSTI in the year prior to swab collection was associated with *S. aureus* colonisation at any site and at any density, with colonisation of the skin at any density, and with heavy nasal colonisation (**Table 35**).

In the multivariable analyses, SSTI in the first five years of life was associated with *S. aureus* colonisation at any site and at any density (aRR 1.09, 95% CI 1.01 – 1.19), but not with heavy nasal colonisation (aRR 1.06, 95% CI 0.91 – 1.22), nor with any skin colonisation (aRR 1.12, 95% CI 0.95 – 1.30) (**Table 34**). SSTI in the year prior to swab collection was associated with *S. aureus* colonisation at any site and at any density (aRR 1.18, 95% CI 1.02 – 1.37), with heavy nasal colonisation (aRR 1.35, 95% CI 1.06 – 1.68), and with skin colonisation (aRR 1.47, 95% CI 1.14 – 1.84) (**Table 35**). Covariates describing Māori or Pacific ethnicity, eczema, and household crowding were significant in all of the models.

7.4 DISCUSSION

This study, performed within a large and diverse birth cohort, has shown that *S. aureus* colonisation is common, that NZ children experience a high rate of SSTI, often requiring hospitalisation, and that there is an association between *S. aureus* colonisation and an increased risk of community-onset SSTI. These associations were more apparent in the year prior to swab collection, consistent with the dynamic nature of *S. aureus* colonisation (220). The link between *S. aureus* nasal colonisation and infection is well established, but convincing evidence that colonisation precedes infection has only been provided in the healthcare setting. The current study is, to the best of our knowledge, the first to estimate the magnitude of the risk that *S. aureus* colonisation poses for development of community-onset SSTI. Ethnic and socioeconomic disparities in SSTI rates, a persistent feature of the epidemiology of infectious disease in NZ (1), remained significant after adjustment for *S. aureus* colonisation status.

Rates of hospitalisation for SSTI, at 702/100,000 children/year overall, and 881 and 1911/100,000 children/year for Māori and Pacific children respectively, were high in comparison with the United States (91/100,000 children/year amongst children aged 0-17 years) (15) and Australia (200/100,000 children/year for non-Aboriginal, and 2600/100,000 children/year for Aboriginal children aged 0-2 years) (9). However, these rates were consistent with previous estimates and with reported increases in SSTI hospitalisations in NZ over recent years (4, 7, 62, 104). The incidence of non-hospitalised SSTI was at least 8 times higher but almost certainly underestimated the burden of community SSTI due to the interview frequency and the wording of interview questions. Previous NZ studies have estimated a ratio of up to 14 SSTIs managed in primary care for every child hospitalised with an SSTI (21).

In all multivariable models, Māori or Pacific ethnicity and a history of eczema remained independent determinants of SSTI after adjustment for *S. aureus* colonisation status. The relationship with eczema is unsurprising – eczema provides an ecological niche for *S. aureus* colonisation and creates breaches the skin barrier increasing the risk of infection. The relationship between Māori or Pacific ethnicity and an increased risk of SSTI has been well documented in NZ (14, 21, 218). Māori and Pacific New Zealanders experience greater exposure to adverse social determinants of health which likely contributes to their increased risk for many infectious diseases. Other potential contributors to this ethnic disparity include reduced access to healthcare and reduced quality of healthcare when accessed (216).

S. aureus was identified at one or more swab sites in 43.4% of the cohort children. The oropharynx is increasingly recognised as an important site of *S. aureus* colonisation; our study confirms that *S. aureus* can be readily recovered from the oropharynx in young children at rates similar to the anterior nares (233). While there were correlations between colonisation at the three sites, almost half the children with oropharyngeal colonisation, and a third of those with skin colonisation, did not have nasal colonisation identified.

The prevalence of heavy nasal colonisation, suggestive of persistent colonisation, was 8.7%. There have been few previous estimates of persistent, rather than cross-sectional, nasal colonisation prevalence in preschool aged children. Our estimate is lower than that of Blumental *et al*., who estimated persistent carriage at 15% in children aged 3-6 years (234).

Heavy nasal colonisation was associated with European ethnicity and socioeconomic deprivation, but was negatively associated with Asian or Pacific ethnicity. Previous studies have also identified higher rates of nasal colonisation amongst European or White participants compared with indigenous peoples in Australia (235), and with non-White participants in the United States (236). The direction of this relationship is opposite to that of SSTI, which may have reduced the apparent effect of nasal colonisation on SSTI outcomes through confounding. Host genetic variation has a significant role in nasal colonisation (226, 227), and this counterintuitive ethnic relationship would support a genetic explanation. *Growing Up in New Zealand* has collected genetic samples so is well placed to contribute to future research investigating the host contribution to *S. aureus* colonisation.

S. aureus colonisation of the antecubital fossa skin was associated with eczema, Pacific ethnicity, and household crowding. The antecubital fossa is a common place for eczematous lesions to develop which may have improved the yield of *S. aureus* from the skin of children with eczema. Household crowding may offer increased opportunities for spread of *S. aureus* through skin contact or fomites, and an increased chance of there being a persistent carrier in the household. Residual confounding may account for some of the increased risk for Pacific children, as over 70% of Pacific children in the cohort lived in a crowded house at some stage during the first 4½ years of life. Host genetics could also play a role and the genetic variants predisposing towards skin colonisation are thought to differ from those predisposing to nasal colonisation (237).

Key strengths of this study include the use of a large cohort which closely matches the contemporary NZ birth cohort, with high rates of swab completeness and consent to linkage to administrative datasets. Our findings may be generalisable to other countries with marginalised ethnic groups, including indigenous peoples, affected by disparities in the social determinants of disease and in rates of SSTI. This study has some limitations. Colonisation was studied at only one time point. In the absence of results from repeated samples, a heavy density of *S. aureus* from the anterior nares was used as a proxy for persistent nasal colonisation (43). Density of growth was determined by an imprecise measure – visual assessment. Despite this, heavy nasal colonisation had a prevalence and relationship to European ethnicity that was consistent with previous research (235, 236). Further bacterial swab samples are being collected at 8 years of age and will help to validate this definition of

persistent colonisation. Rates of SSTI and eczema were based on caregiver report and no information was available on specific diagnoses. As interviewers were not medically trained and survey length had to be controlled, little instruction was provided regarding these diagnoses. Caregiver over-diagnosis and uncertainty about the difference between SSTI and eczema could have strengthened the relationship observed between the two conditions.

In summary, this study has shown that *S. aureus* colonisation is associated with community-onset SSTI in a large sample of preschool children in NZ. This finding suggests that interventions that reduce *S. aureus* nasal or skin colonisation may in turn reduce the rate of SSTI in NZ children. Further studies are needed to assess such interventions, and to inform our understanding of host and bacterial genetic factors that support colonisation at various body sites, which might explain some of the ethnic differences observed in colonisation rates. However, genetic variation is unlikely to explain the ethnic differences in SSTI rates given the large ethnic disparities in the social determinants of health in NZ. Further information is also needed regarding the influence of behavioural and environmental factors on *S. aureus* colonisation, particularly of the skin. If significant behavioural differences with an influence on colonisation are found, they could then inform potential interventions. As the community burden of SSTI is significantly larger than the hospitalised burden, future interventional research should target children presenting to primary care.

7.5 TABLES

Table 29: List of International Statistical Classification of Diseases and Related Health Problems 10th Revision, Australian Modification (ICD-10-AM) codes used to identify hospital discharges for skin and soft tissue infection. ICD-10-AM codes differ from standard ICD-10 codes in not having a decimal point prior to the third digit.

ICD-10-AM Code	Diagnosis
A260, A269	Erysipeloid
A46	Erysipelas
B86	Scabies
H000, H001	Hordeolum and chalazion
H031, H038	Involvement of eyelid in other diseases classified elsewhere
H050	Acute inflammation of orbit
H600, H601, H602, H603, H609	Otitis externa
H610	Perichondritis of external ear
H620, H622, H623, H624	Otitis externa in (bacterial/viral/mycoses/other) diseases classified elsewhere
L01, L010, L011	Impetigo
L02, L020, L021, L022, L023, L024, L028, L029	Cutaneous abscess, furuncle and carbuncle
L03, L030, L031, L032, L033, L038, L039	Cellulitis
L04, L040, L041, L042, L043, L048, L049	Acute lymphadenitis
L050	Pilonidal cyst with abscess
L08, L080, L081, L088, L089	Other local infections of skin and subcutaneous tissue
L303	Infective dermatitis
N482	Other inflammatory disorders of penis
N499	Inflammatory disorder of unspecified male genital organ
N61	Inflammatory disorders of breast
N764	Abscess of vulva

Table 30: Correlations between colonisation of the anterior nares, oropharynx, and antecubital fossa skin with *Staphylococcus aureus* for 4813 children swabbed at all three sites. P-value for all correlations <0.001.

Colonisation site A	**Total colonised at that site, n (%)**	**Colonisation site B**		
		Anterior nares, n (%, phi)	Oropharynx, n (%, phi)	Antecubital fossa skin, n (%, phi)
Anterior nares	1399 (29.1)		661 (47.3, 0.27)	164 (11.7, 0.19)
Oropharynx	1355 (28.2)	661 (48.8, 0.27)		128 (9.5, 0.12)
Antecubital fossa skin	244 (5.1)	164 (67.2, 0.19)	128 (52.5, 0.12)	

Table 30 footnote: The percentages displayed are the proportion of children colonised at site A who are also colonised at site B. Phi = Pearson correlation coefficient

Table 31: Unadjusted and multivariable log-binomial regression adjusted associations between demographic, maternal, perinatal, and household factors and *Staphylococcus aureus* colonisation of the anterior nares, oropharynx, or antecubital fossa skin at any density of growth

		***S. aureus* colonisation at any site and any density**		
Explanatory variable	**Total, n (%)**	**Colonised, n (%)**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
Total	5126 (100)	2225 (43.4)		
Child factors				
Child ethnicity				
European / Other	3200 (62.4)	1404 (43.9)	Reference	Reference
Māori	613 (12.0)	267 (43.6)	0.99 (0.90 – 1.10)	Removed
Pacific	722 (14.1)	314 (43.5)	0.99 (0.90 – 1.09)	Removed
Asian	591 (11.5)	240 (40.6)	0.93 (0.83 – 1.03)	Removed
Male gender	2629 (51.3)	1156 (44.0)	1.03 (0.96 – 1.09)	Removed
History of eczema [a]	1171 (22.8)	601 (51.3)	1.25 (1.17 – 1.34)***	1.25 (1.17 – 1.33)***
Maternal factors				
Maternal age <25 [b]	886 (17.3)	387 (43.7)	1.01 (0.93 – 1.09)	Removed
Maternal education secondary or below [b]	1473 (28.7)	677 (46.0)	1.08 (1.01 – 1.16)*	1.08 (1.01 – 1.16)*
Birth and perinatal factors				
Gestational age <37 weeks	318 (6.2)	141 (44.3)	1.02 (0.90 – 1.16)	Removed
Birth weight <2500 g at term	77 (1.5)	28 (36.4)	0.84 (0.62 – 1.12)	Removed
Delivery by Caesarean section	1229 (24.0)	523 (42.6)	0.97 (0.90 – 1.05)	Removed
Total breastfeeding <6 months	1736 (33.9)	743 (42.8)	0.98 (0.92 – 1.05)	Removed

Table 31 continued		***S. aureus* colonisation at any site and any density**		
Explanatory variable	**Total, n (%)**	**Colonised, n (%)**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
Household factors				
Socioeconomic deprivation [c]	2072 (40.4)	933 (45.0)	1.06 (1.00 – 1.13)	Removed
Household crowding [c]	1512 (29.5)	641 (42.4)	0.97 (0.90 – 1.04)	Removed
Household smoking [c]	1839 (35.9)	809 (44.0)	1.02 (0.96 – 1.09)	Removed
Rural residence [c]	589 (11.5)	247 (41.9)	0.96 (0.87 – 1.06)	Removed

Table 31 footnote: 'Removed' = either excluded from multivariable model due to P>0.15 in unadjusted analysis, or removed during model fitting process guided by the Akaike information criterion. [a] at 4.5 year interview; [b] at antenatal interview; [c] at any interview; RR risk ratio; * P<0.05; ** P<0.01; *** P<0.001; NS not significant (P>0.05)

Table 32: Unadjusted and multivariable log-binomial regression adjusted associations between demographic, maternal, perinatal, and household factors and *Staphylococcus aureus* colonisation of the anterior nares at a heavy density of growth

	***S. aureus* colonisation of the anterior nares at a heavy density**			
Explanatory variable	**Exposed, n(%)**	**Colonised, n(%)**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
Total	5007 (100)	435 (8.7)		
Child factors				
Child ethnicity				
European / Other	3123 (62.4)	313 (10.0)	Reference	Reference
Māori	599 (12.0)	57 (9.5)	0.95 (0.73 – 1.24)	Removed
Pacific	704 (14.1)	39 (5.5)	0.55 (0.40 – 0.76)***	0.60 (0.42 – 0.83)**
Asian	581 (11.6)	26 (4.5)	0.45 (0.30 – 0.66)***	0.50 (0.33 – 0.72)***
Male gender	2564 (51.2)	227 (8.9)	1.04 (0.87 – 1.24)	Removed
History of eczema [a]	1148 (22.9)	104 (9.1)	1.06 (0.86 – 1.30)	Removed
Maternal factors				
Maternal age <25 [b]	860 (17.2)	73 (8.5)	0.97 (0.76 – 1.24)	Removed
Maternal education secondary or below [b]	1445 (28.9)	133 (9.2)	1.09 (0.89 – 1.32)	Removed
Birth and perinatal factors				
Gestational age <37 weeks	310 (6.2)	30 (9.7)	1.12 (0.79 – 1.60)	Removed
Birth weight <2500 g at term	76 (1.5)	<10 (4.0)	0.45 (0.15 – 1.37)	Removed
Delivery by Caesarean section	1201 (24.0)	98 (8.2)	0.92 (0.74 – 1.14)	Removed
Total breastfeeding <6 months	1699 (33.9)	137 (8.1)	0.90 (0.74 – 1.09)	Removed

Table 32 continued	***S. aureus* colonisation of the anterior nares at a heavy density**			
Explanatory variable	**Exposed, n(%)**	**Colonised, n(%)**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
Household factors				
Socioeconomic deprivation [c]	2024 (40.4)	191 (9.4)	1.15 (0.96 – 1.38)	1.32 (1.09 – 1.59)**
Household crowding [c]	1484 (29.6)	95 (6.4)	0.66 (0.53 – 0.83)***	0.73 (0.57 – 0.92)**
Household smoking [c]	1796 (35.9)	160 (8.9)	1.04 (0.86 – 1.25)	Removed
Rural residence [c]	578 (11.5)	61 (10.6)	1.25 (0.97 – 1.62)	Removed

Table 32 Footnote: 'Removed' = either excluded from multivariable model due to P>0.15 in unadjusted analysis, or removed during model fitting process guided by the Akaike information criterion. [a] at 4.5 year interview. [b] at antenatal interview. [c] at any interview. * P<0.05, ** P<0.01, *** P<0.001, NS not significant (P>0.05).

Table 33: Unadjusted and multivariable log-binomial regression adjusted associations between demographic, maternal, perinatal, and household factors and *Staphylococcus aureus* colonisation of the antecubital fossa skin at any density of growth

	***S. aureus* colonisation of the skin at any density**			
Explanatory variable	**Exposed, n(%)**	**Colonised, n(%)**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
Total	5106 (100)	262 (5.1)		
Child factors				
Child ethnicity				
European / Other	3188 (62.4)	133 (4.2)	Reference	Reference
Māori	610 (12.0)	38 (6.2)	1.49 (1.05 – 2.12)*	Removed
Pacific	718 (14.1)	62 (8.6)	2.07 (1.55 – 2.77)***	1.56 (1.15 – 2.09) **
Asian	590 (11.6)	29 (4.9)	1.18 (0.80 – 1.74)	Removed
Male gender	2619 (51.3)	137 (5.2)	1.04 (0.82 – 1.32)	Removed
History of eczema [a]	1161 (22.7)	122 (10.5)	2.96 (2.34 – 3.74)***	2.91 (2.30 – 3.67) ***
Maternal factors				
Maternal age <25 [b]	883 (17.3)	54 (6.1)	1.24 (0.93 – 1.66)	Removed
Maternal education secondary or below [b]	1469 (28.8)	89 (6.1)	1.27 (0.99 – 1.63)	Removed
Birth and perinatal factors				
Gestational age <37 weeks	313 (6.1)	15 (4.8)	0.93 (0.56 – 1.55)	Removed
Birth weight <2500 g at term	77 (1.5)	<10 (1.3)	0.25 (0.04 – 1.76)	Removed
Delivery by Caesarean section	1226 (24.0)	64 (5.2)	1.02 (0.78 – 1.35)	Removed
Total breastfeeding <6 months	1726 (33.9)	94 (5.5)	1.10 (0.86 – 1.40)	Removed

Table 33 continued	***S. aureus* colonisation of the skin at any density**			
Explanatory variable	**Exposed, n(%)**	**Colonised, n(%)**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
Household factors				
Socioeconomic deprivation [c]	2065 (40.4)	126 (6.1)	1.36 (1.08 – 1.73) **	Removed
Household crowding [c]	1508 (29.5)	104 (6.9)	1.57 (1.24 – 2.00) ***	1.34 (1.03 – 1.74) *
Household smoking [c]	1833 (35.9)	115 (6.3)	1.40 (1.10 – 1.77) **	Removed
Rural residence [c]	586 (11.5)	18 (3.1)	0.57 (0.36 – 0.91) *	Removed

Table 33 Footnote: 'Removed' = either excluded from multivariable model due to P>0.15 in unadjusted analysis, or removed during model fitting process guided by the Akaike information criterion. [a] at 4.5 year interview. [b] at antenatal interview. [c] at any interview. * P<0.05, ** P<0.01, *** P<0.001, NS not significant (P>0.05).

Table 34: Unadjusted and multivariable log-binomial regression adjusted associations of *Staphylococcus aureus* colonisation status, demographic, maternal, perinatal, and household factors, with a composite outcome of hospitalised or parent-reported skin and soft tissue infection (SSTI) in the first five years of life.

Explanatory variable	**N (%)**	**SSTI outcome**		**Unadjusted**	**Adjusted RR (95% CI), by site and density of colonisation**		
		Yes, n (%)	**No, n (%)**	**RR (95% CI)**	**Any colonisation**	**Heavy nasal**	**Any skin**
Total	5126 (100)	1509 (29.4)	3617 (70.6)				
***S. aureus* colonisation status**							
Any site and density (n=5126)	2225 (43.4)	694 (31.2)	1531 (68.8)	1.11 (1.02 – 1.21)*	1.09 (1.01 – 1.19)*	Excluded	Excluded
Heavy nasal colonisation (n=5007)	435 (8.7)	133 (30.6)	302 (69.4)	1.04 (0.90 – 1.21)	Excluded	1.06 (0.91 – 1.22)	Excluded
Any skin colonisation (n=5106)	262 (5.1)	97 (37.0)	165 (63.0)	1.27 (1.08 – 1.50)**	Excluded	Excluded	1.12 (0.95 – 1.30)
Child factors							
Child ethnicity							
European / Other	3200 (62.4)	834 (26.1)	2366 (73.9)	Reference	Reference	Reference	Reference
Māori	613 (12.0)	255 (41.6)	358 (58.4)	1.60 (1.43 – 1.78)***	1.46 (1.30 – 1.64)***	1.45 (1.28 – 1.63)***	1.45 (1.29 – 1.63)***
Pacific	722 (14.1)	305 (42.2)	417 (57.8)	1.62 (1.46 – 1.80)***	1.44 (1.28 – 1.62)***	1.43 (1.27 – 1.61)***	1.42 (1.26 – 1.60)***
Asian	591 (11.5)	115 (19.5)	476 (80.5)	0.75 (0.63 – 0.89)***	0.71 (0.59 – 0.84)***	0.72 (0.60 – 0.85)***	0.71 (0.59 – 0.84)***
Male gender	2629 (51.3)	808 (30.7)	1821 (69.3)	1.09 (1.01 – 1.19)*	1.09 (1.00 – 1.18)*	1.10 (1.01 – 1.20)*	1.09 (1.00 – 1.19)*
History of eczema [a]	1171 (22.8)	422 (36.0)	749 (64.0)	1.31 (1.20 – 1.44)***	1.28 (1.17 – 1.40)***	1.29 (1.18 – 1.41)***	1.28 (1.16 – 1.40)***
Maternal factors							
Maternal age <25 [b]	886 (17.3)	324 (36.6)	562 (63.4)	1.31 (1.18 – 1.45)***	Removed	Removed	Removed
Maternal education secondary or below [b]	1473 (28.7)	479 (32.5)	994 (67.5)	1.15 (1.05 – 1.26)**	Removed	Removed	Removed

Table 34 continued	**N (%)**	**SSTI outcome**		**Unadjusted**	**Adjusted RR (95% CI), by site and density of colonisation**		
Explanatory variable		**Yes, n (%)**	**No, n (%)**	**RR (95% CI)**	**Any colonisation**	**Heavy nasal**	**Any skin**
Birth and perinatal factors							
Gestational age <37 weeks	318 (6.2)	93 (29.3)	225 (70.8)	0.99 (0.83 – 1.18)	Removed	Removed	Removed
Birth weight <2500 g at term	77 (1.5)	17 (22.1)	60 (77.9)	0.75 (0.49 – 1.14)	Removed	Removed	Removed
Delivery by Caesarean section	1229 (24.0)	335 (27.3)	894 (72.7)	0.90 (0.82 – 1.00)	Removed	Removed	Removed
Total breastfeeding <6 months	1736 (33.9)	496 (28.6)	1240 (71.4)	0.96 (0.87 – 1.05)	Removed	Removed	Removed
Household factors							
Socioeconomic deprivation [c]	2072 (40.4)	713 (34.4)	1359 (65.6)	1.32 (1.21 – 1.44)***	1.10 (1.01 – 1.21)	1.10 (1.00 – 1.20)	1.11 (1.01 – 1.21)*
Household crowding [c]	1512 (29.5)	539 (35.7)	973 (64.4)	1.33 (1.22 – 1.45)***	1.13 (1.03 – 1.25)*	1.13 (1.02 – 1.25)*	1.12 (1.02 – 1.24)*
Household smoking [c]	1839 (35.9)	631 (34.3)	1208 (65.7)	1.28 (1.18 – 1.40)***	Removed	Removed	Removed
Rural residence [c]	589 (11.5)	167 (28.4)	422 (71.7)	0.96 (0.84 – 1.10)	Removed	Removed	Removed

Table 34 footnote: 'Removed' = either excluded from multivariable model due to P>0.15 in unadjusted analysis, or removed during model fitting process guided by the Akaike information criterion.[a] at 4.5 year interview. [b] at antenatal interview. [c] at any interview. RR risk ratio. * P<0.05. ** P<0.01. *** P<0.001.

Table 35: Unadjusted and multivariable log-binomial regression adjusted associations of *Staphylococcus aureus* colonisation status, demographic, maternal, perinatal, and household factors, with a composite outcome of hospitalised or parent-reported skin and soft tissue infection (SSTI) in the year prior to microbiological sampling at 4½ years of age.

Explanatory variable	**N (%)**	**SSTI outcome**		**Unadjusted**	**Adjusted RR (95% CI), by site and density of colonisation**		
		Yes, n (%)	**No, n (%)**	**RR (95% CI)**	**Any colonisation**	**Heavy nasal**	**Any skin**
Total	5126 (100)	629 (12.3)	4497 (87.7)				
***S. aureus* colonisation status**							
Any site and density	2225 (43.4)	303 (13.6)	1922 (86.4)	1.21 (1.05 – 1.40)*	1.18 (1.02 – 1.37)*	Excluded	Excluded
Heavy nasal colonisation	435 (8.7)	68 (15.6)	367 (84.4)	1.29 (1.02 – 1.63)*	Excluded	1.35 (1.06 – 1.68)*	Excluded
Any skin colonisation	262 (5.1)	57 (21.8)	205 (78.2)	1.85 (1.45 – 2.35)***	Excluded	Excluded	1.47 (1.14 – 1.84)**
Child demographics							
Child ethnicity							
European / Other	3200 (62.4)	323 (10.1)	2877 (89.9)	Reference	Reference	Reference	Reference
Māori	613 (12.0)	127 (20.7)	486 (79.3)	2.05 (1.70 – 2.47)***	1.83 (1.50 – 2.23)***	1.83 (1.49 – 2.23)***	1.79 (1.46 – 2.17)***
Pacific	722 (14.1)	135 (18.7)	587 (81.3)	1.85 (1.54 – 2.23)***	1.61 (1.30 – 1.98)***	1.64 (1.32 – 2.03)***	1.59 (1.28 – 1.96)***
Asian	591 (11.5)	44 (7.5)	547 (92.6)	0.74 (0.55 – 1.00)*	0.67 (0.49 – 0.90)*	0.69 (0.50 – 0.92)*	0.67 (0.49 – 0.91)*
Male gender	2629 (51.3)	340 (12.9)	2289 (87.1)	1.12 (0.96 – 1.29)	Removed	Removed	Removed
History of eczema [a]	1171 (22.8)	208 (17.8)	963 (82.2)	1.67 (1.43 – 1.94)***	1.60 (1.37 – 1.85)***	1.62 (1.39 – 1.88)***	1.57 (1.35 – 1.83)***
Maternal factors							
Maternal age <25 [b]	886 (17.3)	130 (14.7)	756 (85.3)	1.25 (1.04 – 1.49)*	Removed	Removed	Removed
Maternal education secondary or below [b]	1473 (28.7)	188 (12.8)	1285 (87.2)	1.06 (0.90 – 1.24)	0.83 (0.70 – 0.97) *	0.83 (0.70 – 0.98) *	0.83 (0.70 – 0.98)*

Table 4 continued	**N (%)**	**SSTI outcome**		**Unadjusted**	**Adjusted RR (95% CI), by site and density of colonisation**		
Explanatory variable		**Yes, n (%)**	**No, n (%)**	**RR (95% CI)**	**Any colonisation**	**Heavy nasal**	**Any skin**
Birth and perinatal factors							
Gestational age <37 weeks	318 (6.2)	47 (14.8)	271 (85.2)	1.22 (0.93 – 1.61)	Removed	Removed	Removed
Birth weight <2500 g at term	77 (1.5)	<10 (7.8)	71 (92.2)	0.63 (0.29 – 1.37)	Removed	Removed	Removed
Delivery by Caesarean section	1229 (24.0)	143 (11.6)	1086 (88.4)	0.93 (0.78 – 1.11)	Removed	Removed	Removed
Total breastfeeding <6 months	1736 (33.9)	219 (12.6)	1517 (87.4)	1.04 (0.89 – 1.22)	Removed	Removed	Removed
Household factors							
Socioeconomic deprivation [c]	2072 (40.4)	316 (15.3)	1756 (84.8)	1.49 (1.29 – 1.72)***	1.19 (1.01 – 1.39)*	1.18 (1.00 – 1.38)*	1.19 (1.01 – 1.39)*
Household crowding [c]	1512 (29.5)	241 (15.9)	1271 (84.1)	1.48 (1.28 – 1.72)***	1.22 (1.03 – 1.46)*	1.23 (1.03 – 1.46)*	1.21 (1.01 – 1.44)*
Household smoking [c]	1839 (35.9)	273 (14.9)	1566 (85.2)	1.37 (1.18 – 1.59)***	Removed	Removed	Removed
Rural residence [c]	589 (11.5)	62 (10.5)	527 (89.5)	0.84 (0.66 – 1.08)	Removed	Removed	Removed

Table 4 footnote: 'Removed' = either excluded from multivariable model due to P>0.15 in unadjusted analysis, or removed during model fitting process guided by the Akaike information criterion. [a] at 4.5 year interview, [b] at antenatal interview, [c] at any interview, RR risk ratio. * P<0.05, ** P<0.01, *** P<0.001, NS not significant (P>0.05)

CHAPTER 8: METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* COLONISATION AND RISK OF SKIN AND SOFT TISSUE INFECTION IN NEW ZEALAND CHILDREN

In Chapter 7, colonisation of the nose, throat, or skin with *Staphylococcus aureus* was found to be associated with a small increased risk of community-onset SSTI. The relative risk estimates were larger for the associations between SSTI and colonisation of the skin, and between SSTI in the year prior to swab collection and colonisation either at any site or on the skin. Chapter 8 looks in further detail within the subgroup of children colonised with *S. aureus*, to determine whether colonisation with a methicillin-resistant strain (MRSA) carried a higher risk of community-onset SSTI when compared with colonisation with a methicillin-susceptible strain. Based on results from Chapter 7, a further abbreviated list of explanatory covariates was used, and SSTI outcomes were limited to the year prior to the interview conducted at 4½ years of child age.

Colonisation with an MRSA strain of *S. aureus* was associated with Māori or Pacific ethnicity, and with socioeconomic deprivation and household crowding. MRSA colonisation was associated with an increased risk of SSTI compared with colonisation with a methicillin-susceptible strain. The finding that MRSA colonisation was associated with an increased risk of SSTI suggested that there might be meaningful differences between colonising strains of *S. aureus* with regards to their propensity to cause community-onset SSTI. However, an alternative explanation for this finding would be that the reported SSTI led to a course of antibiotics being prescribed which increased the risk of the child subsequently becoming colonised with an antibiotic-resistant organism. Further research is required to determine which of these scenarios is predominant although it would be possible for both to be true.

8.1 INTRODUCTION

Community-acquired methicillin-resistant *Staphylococcus aureus* (caMRSA) has become an increasingly common cause of skin and soft tissue infection (SSTI). In the United States, the Panton-Valentine leucocidin (PVL) producing USA300 caMRSA strain has expanded rapidly in recent decades (116), while in New Zealand (NZ), the fusidic acid resistant, PVL-negative AK3 caMRSA strain has become predominant (238). Previous studies from NZ have shown that amongst people with swab cultures positive for *S. aureus* at a community laboratory, Māori and Pacific people were more likely to have an MRSA strain detected (22). Here we seek to determine the factors associated with colonisation with an MRSA strain, and whether colonisation with an MRSA strain is associated with a greater risk of SSTI prior to 4½ years of age than colonisation with a methicillin-susceptible *S. aureus* (MSSA) strain.

8.2 METHODS

This study was performed within the *Growing up in New Zealand* longitudinal child cohort which comprises 6853 children born in 2009 and 2010. The cohort has high retention rates, and is generalizable to the national birth cohort with regards to ethnicity and socioeconomic deprivation (37-39). Ethical approval was obtained from the Ministry of Health Northern Y Regional Ethics Committee (NTY/08106/055) and primary caregivers provided informed consent to biological sampling and linkage with administrative health data. Interviews were conducted with each child's primary caregiver at 4½ years of child age, at which trained interviewers collected Copan eSwabs (Brescia, Italy) from the anterior nares, oropharynx, and antecubital fossa of participating children. Swab culture was performed by a community medical laboratory in Auckland, NZ. Suspected isolates of *S. aureus* were identified using mass spectrometry (MALDI-TOF, BD Bruker Biotyper, Becton, Dickinson and Company, Franklin Lakes, NJ, USA). Antimicrobial susceptibilities were determined using disc diffusion and were interpreted using Clinical and Laboratory Standards Institute (CLSI) criteria (231), with cefoxitin resistance used to define MRSA status.

Outcomes of interest included colonisation at any site with an MRSA isolate, and SSTI. SSTI was defined using a composite of one or more hospitalisations for an SSTI or one or more

caregiver-reported SSTIs in the year prior to the interview at 4½ years of age. Explanatory variables were also obtained from the interview conducted at 4½ years of age and included the single main ethnicity identified for the child by their primary caregiver, parent-reported diagnosis of eczema, socioeconomic deprivation (defined as an NZiDep score of ≥3) (50), and household crowding (defined as a ratio of occupants to bedrooms of ≥2). Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, U.S.A.). Analyses were restricted to children who were *S. aureus*-colonised. Unadjusted associations were described using relative risks (RR), while adjusted relative risks (aRR) corrected for explanatory variables were derived from multivariable analyses using log-binomial regression. All explanatory variables were included with no additional model fitting performed.

8.3 RESULTS

8.3.1 Study sample and associations with MRSA colonisation status

Complete data from the interview at 4½ years of age, linked hospitalisation data, and bacterial swab culture results were available for 5291 children, of whom 2295 (43.4%) were colonised at one or more sites with *S. aureus*. Of these 2295 *S. aureus*-colonised children, 194 (8.5%) were colonised with an MRSA strain and the remaining 2101 (91.6%) were colonised with an MSSA strain. After adjustment for covariates, children of Māori (aRR 3.45, 95% CI 2.39 – 4.97, p<0.0001) and Pacific ethnicity (aRR 3.13, 95% CI 2.16 – 4.53, p<0.0001) had a greater risk that their colonising strain of *S. aureus* was methicillin resistant (**Table 36**). Socioeconomic deprivation and household crowding were also significantly associated with MRSA colonisation.

8.3.2 Associations between MRSA colonisation status and risk of SSTI

Of the 2295 *S. aureus* colonised children, 316 (13.8%) had an SSTI in the year prior to the interview at 4½ years of age, including 14 (0.6%) who were admitted to hospital with an SSTI. After adjustment for covariates, the period-prevalence of SSTI in the preceding year, was 1.45 times higher in children colonised with an MRSA strain (48/194; 24.7%) than in children colonised with an MSSA strain 268/2101 (12.8%) (p=0.008) (**Table 37**). The period-

prevalence of a hospital admission for an SSTI was 4.33 times higher in children colonised with an MRSA strain (4/194; 2.1%) than in children colonised with an MSSA strain (10/2101, 0.5%) (95% CI 1.37 – 13.68, p=0.03). Māori and Pacific children, children with eczema, and children in more socioeconomically deprived households were more likely to have had an SSTI independent of MRSA status.

8.4 DISCUSSION

MRSA colonisation was more common amongst Māori and Pacific children, and children in more socioeconomically deprived or crowded households. The reasons why MRSA strains were more likely to colonise Māori and Pacific people than people of European/Other ethnicities are unclear. The Māori and Pacific populations in NZ are exposed to range of adverse social determinants of health, including a greater degree of household crowding which might be expected to facilitate the spread of *S. aureus* within households, but there is no reason we are aware of why these factors should favour colonisation by MRSA strains over MSSA strains. African-American children in the USA have also been shown to be more likely to be colonised with a caMRSA strain (239); and it possible that similar social factors underlie this finding. Previous research has identified a number of modifiable behavioural factors, such as sharing washcloths and ointments, which were associated with MRSA colonisation amongst household contacts of a case of MRSA infection (240).

MRSA colonisation was independently associated with an increased risk of SSTI. The increased rate of SSTI seen in children colonised with an MRSA strain is consistent with previous research using clinical isolates of *S. aureus*, which showed that Māori and Pacific people in NZ (22), and African-Americans in the USA (119), were more likely to have a methicillin-resistant isolate identified. Children colonised with an MRSA strain made up 28.6% of those admitted to hospital with an SSTI in this study, although this should not be interpreted as suggesting that MRSA caused these SSTIs, as this study did not have access to clinical isolates. Previous research in a large NZ hospital showed that MRSA causes approximately 13% of childhood SSTIs which require hospital admission (62). MRSA strains are responsible for a much greater proportion of hospitalisations in the USA, where a majority

of children admitted to hospital with a culture-positive purulent SSTI now have an MRSA isolate (most commonly of the USA300 strain) (33, 117, 241).

The receipt of antibiotics in the community likely plays a key role in the findings of this study. Previous research in the *Growing Up in New Zealand* cohort showed that Māori and Pacific children received more courses of antibiotics prior to 5 years of age (242). There is good evidence that exposure to antibiotics promotes the spread of antibiotic-resistant clones of bacteria (243-245). Prior receipt of antibiotics has been specifically linked to MRSA infection in Native Hawaiians and Pacific Islanders in Hawaii (246), and in children in the United Kingdom (247). The high number of courses of antibiotics given to Māori and Pacific children in NZ might therefore partly explain their higher rates of MRSA colonisation. The association between MRSA colonisation and SSTI may have been identified because prior receipt of antibiotics for an SSTI led to an increased risk of MRSA colonisation at the time of swab collection. In NZ anti-staphylococcal penicillins are recommended as first-line for boils (197), and would be expected to provide selective pressure in favour of MRSA. Alternatively, it is possible that colonisation with an MRSA strain, persisting for some time prior to swab collection, led to a higher risk of serious SSTI than colonisation with an MSSA strain, possibly due to the carriage of additional virulence factors by circulating caMRSA strains. PVL is an example of such a virulence factor and has been implicated in causing severe SSTI, although it is not prevalent in NZ caMRSA (31). MRSA strains may be more likely to result in hospital admission due to a greater chance of failure of first-line antibiotics in the community. The current study determined MRSA colonisation at a single time point and detailed data regarding the timing of SSTIs and the use of antibiotics were not available. The separation in time between the detection of MRSA colonisation and the occurrence of an SSTI would be expected to have weakened any association between these events. Further research is required to clarify the exact temporal relationships at the individual level between receiving antibiotics, acquiring MRSA colonisation, and experiencing an SSTI.

Our findings support calls for more judicious prescribing of antibiotics to reduce the spread of antibiotic resistant organisms in our communities. Further research is needed to determine the relationship between receipt of antibiotics and the risk of MRSA colonisation, and whether there are other factors which also affect this risk. Interventional studies are required to determine whether eradication of MRSA carriage leads to a reduced risk of SSTI. If this were

shown to be the case, then targeting eradication treatment to MRSA carriers in high risk groups might help to address the disparities in SSTI rates seen in NZ. Further attention is also needed to address the social determinants of health, which operate independently of MRSA colonisation status.

8.5 TABLES

Table 36: Unadjusted and multivariable adjusted associations between methicillin-resistant *Staphylococcus aureus* (MRSA) colonisation status and explanatory covariates in 2295 *S. aureus* colonised children.

Explanatory covariate	**Colonising *S. aureus* strain**		**Unadjusted associations**		**Multivariable associations**	
	MRSA	**MSSA**	**RR (95% CI)**	**p–value**	**aRR (95% CI)**	**p–value**
Total	194 (8.5)	2101 (91.6)				
Ethnicity						
Māori	52 (18.6)	228 (81.4)	4.34 (3.07 – 6.14)	<0.0001	3.45 (2.39 – 4.97)	<0.0001
Pacific	64 (18.7)	278 (81.3)	4.37 (3.14 – 6.09)	<0.0001	3.13 (2.16 – 4.53)	<0.0001
Asian	17 (6.9)	230 (93.1)	1.61 (0.96 – 2.71)	0.07	1.54 (0.88 – 2.54)	0.11
European/Other	61 (4.3)	1365 (95.7)	Reference		Reference	
Sex						
Male	106 (8.9)	1085 (91.1)	1.12 (0.85 – 1.46)	0.42	1.08 (0.83 – 1.40)	0.57
Female	88 (8.0)	1016 (92.0)	Reference		Reference	
Eczema						
Present	55 (8.8)	570 (91.2)	1.06 (0.78 – 1.42)	0.71	0.98 (0.73 – 1.30)	0.89
Absent	139 (8.3)	1531 (91.7)	Reference		Reference	
NZiDep score						
1 to 2	101 (5.9)	1604 (94.1)	Reference		Reference	
3 to 5	93 (15.8)	497 (84.2)	2.66 (2.04 – 3.47)	<0.0001	1.70 (1.28 – 2.25)	0.0002
Household crowding						
Present	68 (16.2)	352 (83.8)	2.41 (1.83 – 3.17)	<0.0001	1.38 (1.03 – 1.85)	0.03
Absent	126 (6.7)	1749 (93.3)	Reference		Reference	

Table 36 footnote: MRSA methicillin-resistant *Staphylococcus aureus*; MSSA methicillin-susceptible *Staphylococcus aureus*

Table 37: Unadjusted and multivariable adjusted associations between skin and soft tissue infection (SSTI) in the year prior to detection of *Staphylococcus aureus* colonisation at 4½ years of age and explanatory covariates, including methicillin-resistance (MRSA) of the colonising strain, in 2295 *S. aureus* colonised children.

Explanatory covariate	**SSTI outcome**		**Unadjusted associations**		**Multivariable associations**	
	Yes	**No**	**RR (95% CI)**	**p–value**	**aRR (95% CI)**	**p–value**
Total	316 (13.8)	1979 (86.2)				
Colonising *S. aureus* strain						
MRSA	48 (24.7)	146 (75.3)	1.94 (1.48 – 2.54)	<0.0001	1.45 (1.09 – 1.88)	0.008
MSSA	268 (12.8)	1833 (87.2)	Reference		Reference	
Ethnicity						
Māori	69 (24.6)	211 (75.4)	2.22 (1.73 – 2.86)	<0.0001	1.74 (1.33 – 2.27)	<0.0001
Pacific	71 (20.8)	271 (79.2)	1.87 (1.45 – 2.42)	<0.0001	1.51 (1.13 – 1.98)	0.004
Asian	18 (7.3)	229 (92.7)	0.66 (0.41 – 1.05)	0.07	0.60 (0.36 – 0.93)	0.03
European/Other	158 (11.1)	1268 (88.9)	Reference		Reference	
Sex						
Male	168 (14.1)	1023 (85.9)	1.05 (0.86 – 1.29)	0.63	1.01 (0.83 – 1.23)	0.93
Female	148 (13.4)	956 (86.6)	Reference		Reference	
Eczema						
Present	133 (21.3)	492 (78.7)	1.94 (1.58 – 2.38)	<0.0001	1.89 (1.55 – 2.31)	<0.0001
Absent	183 (11.0)	1487 (89.0)	Reference		Reference	
NZiDep score						
1 to 2	202 (11.9)	1503 (88.2)	Reference		Reference	
3 to 5	114 (19.3)	476 (80.7)	1.63 (1.32 – 2.01)	<0.0001	1.26 (1.01 – 1.56)	0.04
Household crowding						
Present	79 (18.8)	341 (81.2)	1.49 (1.18 – 1.88)	0.0009	1.16 (0.91 – 1.48)	0.22
Absent	237 (12.6)	1638 (87.4)	Reference		Reference	

CHAPTER 9: ASSOCIATIONS BETWEEN *STAPHYLOCOCCUS AUREUS* GENOTYPE AND RISK OF SKIN AND SOFT TISSUE INFECTION

Chapter 8 showed that methicillin-resistant *Staphylococcus aureus* (MRSA) colonisation was associated with an increased risk of community-onset SSTI in the year prior to the interview conducted at 4½ years of child age. One interpretation of this finding was that there may have been differences between strains of *S. aureus* with regard to their propensity to cause SSTI. The alternative explanation was that antibiotic treatment for an SSTI led to a greater risk of MRSA colonisation. Chapter 9 sought to extend the findings of Chapters 7 and 8 by looking at whether particular strains of *S. aureus* were associated with a higher risk of SSTI than others. A common method of genotyping strains of *S. aureus*, *spa*-typing, was used to differentiate strains. The list of demographic and environmental covariates that were used in Chapter 8 was retained. Correction for multiple comparisons was performed using the Benjamini-Hochburg procedure.

On unadjusted analyses, several strains of *S. aureus* appeared to be associated with an increased risk of SSTI. However, when covariates were included in the multivariable model and corrections were made for multiple comparisons, there were no significant associations between strain and risk of SSTI. While this study may have been underpowered to detect an effect, this finding suggested that the effect of *S. aureus* strain type on the ethnic and socioeconomic disparities observed in the risk of SSTI was likely to be small, and interventions aiming to reduce rates of SSTI should focus on disparities in the social determinants of health.

9.1 INTRODUCTION

Staphylococcus aureus is a major human pathogen that most commonly causes skin and soft tissue infection (SSTI) but may also cause life-threatening sepsis (248). New Zealand (NZ) children suffer from high rates of SSTI due to *S. aureus*, particularly amongst Māori and Pacific children and in the most socioeconomically deprived areas of the country (5, 7, 104, 218). However, asymptomatic carriage of *S. aureus* in the anterior nares, on the skin, or in the digestive tract is common (40, 220, 221). We have previously shown that *S. aureus* colonisation at 4½ years of age was associated with an increased risk of community-onset SSTI in early childhood in a large cohort of NZ children (249).

Individuals can be classified as persistent carriers, intermittent carriers, or non-carriers, based on carriage patterns of *S. aureus* in the anterior nares (224). Intermittent carriers will carry a given strain of *S. aureus* for a period of weeks or months before eventually clearing it, while persistent carriers are almost always colonised with *S. aureus* and have an increased risk of nosocomial *S. aureus* infection. However, persistent carriage is also dynamic with colonising strains changing over time (220). In general a single strain predominates within a given anatomical site but multiple-strain colonisation can occasionally be detected, perhaps more commonly as strains change (220, 250). In contrast, recent studies looking at *S. aureus* colonisation across multiple anatomical sites have shown that colonisation with discordant strains between sites is common (251, 252).

There is great diversity in the strains of *S. aureus* that may colonise or cause disease in humans, but little evidence that particular strains have an increased propensity to either establish colonisation or cause disease. However, for some diseases caused by *S. aureus*, there are clear associations between disease risk and bacterial genotype due to the carriage of specific virulence genes. For example, *S. aureus* strains from multi-locus sequence type derived clonal complexes 5 and 30 were associated with toxic shock syndrome due to their carriage of the *tst* gene (253, 254). Some, but not all, studies have suggested a relationship between *S. aureus* strains which produce Panton-Valentine leucocidin and severe skin infections (30, 31).

To date most investigations into the molecular epidemiology of *S. aureus* have used clinical isolates rather than colonising isolates from asymptomatic carriers (13, 22). In the present study we aimed to determine whether the risk of SSTI in children with asymptomatic *S. aureus* carriage was dependent on which strain of *S. aureus* the child was colonised with. We hypothesised that there might be variation in the risk of SSTI due to differences in strain virulence, and that if these strains were not homogeneously spread throughout the population this might explain some of the ethnic variation in the rates of SSTI seen in NZ. Further, we hypothesised that colonisation with discordant strains at different anatomical sites might indicate an increased frequency of encountering novel strains due to environmental factors such as household crowding, and might therefore be associated with an increased risk of SSTI.

A range of molecular techniques can be used to differentiate between strains of *S. aureus*, including *spa*-typing and whole genome sequencing (255). Whole genome sequencing provides great detail but remains prohibitively expensive for large population-based studies. *spa* typing, which involves sequencing of the hypervariable region of the staphylococcal protein A gene, offers an inexpensive alternative, albeit with reduced capacity to differentiate strains (44, 45, 256). The Based Upon Repeat Pattern (BURP) algorithm can be used to place related *spa*-types into clonal complexes (*spa*-CCs) which correlate with multi-locus sequence typing clonal complexes with a high degree of concordance (147, 257, 258).

9.2 METHODS

9.2.1 Ethics

Parents provided written informed consent to microbiological sampling, and to linkage with administrative health datasets. Ethical approval was obtained from the Ministry of Health Northern Y Regional Ethics Committee (NTY/08106/055).

9.2.2 Study design, population and sample

This study was performed within the *Growing up in New Zealand* longitudinal child cohort study. The study enrolled 6822 pregnant women and the cohort comprises their 6853 children born in 2009 and 2010. The enrolment methodology and retention rates have been described previously (37). The cohort represents 11% of the national birth cohort and is generalizable to the national birth cohort with regards to ethnicity and socioeconomic deprivation (38, 39). Face-to-face interviews have been conducted with each child's primary caregiver in the antenatal period, at 9 months, and at 2 and 4½ years of child age. At the interview conducted at 4½ years of child age trained interviewers collected Copan eSwabs (Brescia, Italy) from the anterior nares, oropharynx, and antecubital fossa of participating children.

9.2.3 Microbiological sampling and laboratory methods

Swab culture was performed by a single community medical laboratory in Auckland, NZ. Swabs from the anterior nares and antecubital fossa were cultured on tryptic soy sheep blood agar and swabs from the oropharynx were cultured on 3% salt Columbia sheep blood agar. Agar plates were incubated for 48 hours at 35°C in 5% CO_2. Suspected colonies of *S. aureus* were identified using matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry (BD Bruker Biotyper, Becton, Dickinson and Company, Franklin Lakes, New Jersey, U.S.A.). Antimicrobial susceptibilities were determined for isolates of *S. aureus* using disc diffusion and were interpreted using Clinical and Laboratory Standards Institute (CLSI) criteria (231). Isolates were stored at -80°C in Protect TS/80 Cryovials with Micro-organism Preservation Beads (Technical Service Consultants, Heywood, United Kingdom).

To perform *spa* typing a single colony was selected from stored isolates plated onto mannitol salt agar and incubated overnight at 37°C. DNA extraction was performed by incubating with 1 mg/mL lysostaphin (Sigma-Aldrich, St. Louis, MO, USA) at 37°C for 30 minutes, followed by heating to 95°C for 10 minutes, then centrifugation at 13000 RPM for 3 minutes. PCR was performed using standard *spa* forward (5' TAA AGA CGA TCC TTC RGT GAG C) and reverse (5' CAG CAG TAG TGC CGT TTG CT) primers (Sigma-Aldrich). Purification and sequencing of the PCR product was performed by Macrogen Inc. (Seoul, Korea).

Ridom StaphType version 2.2.1 software (Ridom GmbH, Münster, Germany) was used to assign *spa* types and to cluster the *spa*-types into *spa*-CCs using the BURP algorithm (45, 147). The default settings were used, so strains with a repeat region shorter than 5 repeats were not allocated to a *spa*-CC. These strains were included along with singletons, non-typable stains, and strains belonging to rare spa-CCs colonising less than 10 children in a heterogeneous residual category which was used as the comparator group. Discordant strain colonisation was defined as colonisation at more than one site with discordant *spa*-CCs of *S. aureus*. Children with discordant strain colonisation were included in both strain groups in multivariable analyses.

9.2.4 Explanatory variables

Explanatory variables were obtained from the interview conducted when the cohort children were 4½ years old and described child demographics, parental report of eczema diagnosis, socioeconomic deprivation, and household crowding. These variables were included in multivariable models based on significant findings from previous research into SSTI in the cohort. Ethnicity was defined as the main ethnicity identified for the child by their primary caregiver and was aggregated into broad categories – Māori, Pacific, Asian, and a combined comparator group of European and Other ethnicities. Socioeconomic deprivation was measured using the validated NZiDep (2014 update) index (50, 51), based on questionnaire data provided by the primary caregiver. Household crowding was defined as a ratio of household occupants to bedrooms of 2 or greater.

9.2.5 Outcome variables

The primary outcome was a composite endpoint combining documented hospitalisation for an SSTI and/or parental report of an SSTI at any time during the year prior to the 4½ year interview. Hospitalisation for an SSTI was identified using discharge diagnostic codes taken from the National Minimum Dataset (NMDS), a national administrative dataset describing all public hospital admissions. All acute paediatric care in NZ is provided at public hospitals. Diagnoses in the NMDS are coded using the Australian Modification of the ICD-10 (ICD-10-AM). Because the first listed code is intended to represent the main problem managed during that admission, only hospitalisations where the first diagnostic code was for a SSTI were counted.

9.2.6 Statistical analysis

Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, U.S.A.). Because not all *S. aureus* isolates were available for genotyping, analyses were restricted to the portion of the cohort who were *S. aureus*-colonised and who had at least one isolate available for typing. Unadjusted associations with the primary outcome were presented as risk ratios with 95% confidence intervals, and χ^2 p-values. Multivariable analyses were performed using log-binomial regression, with results presented as adjusted risk ratios, 95% confidence intervals and p-values. All explanatory variables were included with no additional model fitting performed. Log-binomial regression was used as the composite primary outcome was not rare and odds ratios from logistic regression would therefore be expected to overestimate the risk ratios. For both unadjusted and multivariable results, the significance of associations between *spa*-types and SSTI was interpreted after correction for multiple comparisons using the Benjamini-Hochburg procedure with a false discovery rate of 10% (259). The other explanatory covariates, which were expected to be associated with the outcome, were not included in the correction.

9.3 RESULTS

9.3.1 Study sample

Complete data from the parental interview at 4½ years of child age, from the linked hospitalisation data, and from the results of culture of the swabs taken from the anterior nares, oropharynx, and antecubital fossa were available for 5235 children, of whom 2267 (43.3%) had *S. aureus* isolated from one or more of the three sites sampled. The sample for this study consisted of the 1332/2267 (58.8%) children for whom one or more isolates of *S. aureus* were available for genotyping. The demographic data for the *S. aureus*-colonised children for whom an isolate was available for genotyping were similar to those for the *S. aureus*-colonised children for whom no *S. aureus* isolate was available (**Table 38**). However, Māori children were more likely to have an isolate available for genotyping while Asian children were less likely to have an isolate available for genotyping. This discrepancy resulted from efforts to enhance recruitment of Māori mothers late in the enrolment period; thus, their children had

swabs taken later in the study period when isolate storage rates were coincidentally higher. Given the high rates of SSTI seen amongst Māori, an oversampling of Māori children in the study is potentially an advantage.

9.3.2 Colonisation rates and sites

Of the 1332 children with one or more colonising isolates available for genotyping, 827 (62.1%) were colonised at one site, 430 (32.3%) at two sites, and 75 (5.6%) at all three sites. Overall, 886 (66.5%) were colonised in the anterior nares, 845 (63.4%) in the oropharynx, and 181 (13.6%) in the antecubital fossa. The majority of colonising isolates from these sites – 781/866 (88.1%) from the anterior nares, 759/845 (89.8%) from the oropharynx, and 166/181 (91.7%) from the antecubital fossa – were available for genotyping.

9.3.3 spa-CCs and spa-types of colonising strains

The most frequently identified *spa*-CCs of the colonising isolates were CC 630 (36.9%) and CC 002 (31.3%) (**Table 39**), and the proportion of predominant *spa*-CCs causing anterior nares, oropharynx and antecubital fossa colonisation was similar. Within *spa*-CC 630, t189 and t127 were the most common *spa*-types (other authors have identified this as *spa*-CC 127) (260), while within *spa*-CC 002, t002 and t1265 were most common. The most frequent individual *spa*-types are shown in **Table 40**.

There was variation in the distribution of *spa*-CCs that colonised children of different ethnicities. For example, Māori and Pacific children were less likely to be colonised with *spa*-CC 275, and Māori children were more likely to be colonised with *spa*-CC 876 (**Table 41**). However, after controlling for multiple comparisons these differences were not statistically significant.

9.3.4 Discordant strain colonisation

Most of the children who were colonised at two or three sites were colonised with the same strain of *S. aureus*. Of 430 children who were colonised at two sites, 266 (61.9%) had both

isolates available for genotyping, of whom 59 (22.2 %) had discordant *spa*-CCs. Likewise, 44/75 (58.7%) children colonised at all three sites had all three isolates available, of whom 15/44 (34.1%) had discordant *spa*-CCs. Of those colonised in both the anterior nares and oropharynx 60/266 (22.6%) had discordant *spa*-CCs at the two sites, as did 18/84 (21.4%) of children colonised in the anterior nares and antecubital fossa, and 19/64 (29.7%) of children in the oropharynx and antecubital fossa. Māori children were more likely to be colonised with discordant strains (RR 1.81, 95% CI 1.04 – 3.15, p=0.03) but otherwise, discordant strain colonisation was not significantly associated with any of the explanatory variables.

9.3.5 Methicillin-resistant S. aureus

Of the 1332 *S. aureus* colonised children, 120 (9.0%) were colonised with an MRSA strain, of whom 117 (98%) had an MRSA isolate available for typing. Colonisation with an MRSA strain was more common in Māori (38/176, 21.6%) and Pacific children (37/195, 19.0%), when compared with European/Other children (35/837, 4.2%) (unadjusted RR 5.16, 95% CI 3.36 – 7.93, and RR 4.54, 95% CI 2.94 – 7.01 respectively, p<0.01 for both). Over 80% of MRSA isolates belonged to *spa*-CC 002 with a smaller number belonging to *spa*-CC 630 (**Table 42)**.

9.3.6 Associations with risk of SSTI

In unadjusted analyses with correction for multiple comparisons, colonisation with *spa*-CC 876 (p<0.01), colonisation with an MRSA strain (p<0.01) and colonisation with multiple strains at different sites (p<0.05) were all associated with an increased risk of SSTI (**Table 43**), while colonisation with any of the other *spa*-CCs was not. In the multivariable analysis that included only *spa*-CCs, *spa*-CC 630, *spa*-CC 002, *spa*-CC 084, and *spa*-CC 876 all appeared to be associated with an increased risk of SSTI. However, when MRSA colonisation, colonisation with multiple strains, and demographic and environmental covariates were accounted for, no *spa*-CCs remained significantly associated with SSTI. Māori (aRR 1.69, 95% CI 1.18 – 2.38, p=0.004) or Pacific ethnicity (aRR 1.48, 95% CI 1.01 – 2.14, p=0.04), and the presence of eczema (aRR 1.83, 95% CI 1.41 – 2.38, p<0.0001) were associated with an increased risk of SSTI, while Asian ethnicity was associated with a decreased risk of SSTI (aRR 0.46, 95% CI 0.20 – 0.89, p=0.04).

9.4 DISCUSSION

This study has looked for an association between the genotype (*spa*-CC) of colonising strains of *S. aureus* and the risk of SSTI while controlling for the influence of a range of host and environmental factors in a large and diverse cohort of NZ children. Previous research within the *Growing Up in New Zealand* cohort identified that colonisation with *S. aureus* was associated with an increased risk of SSTI (249). The relationship was strongest for skin colonisation and for SSTI in the year prior to swab collection. This relationship could have been causal, or *S. aureus* colonisation could have functioned as a marker of risk of SSTI due to unmeasured confounding factors. In the current study, in unadjusted analyses and when only *spa*-CCs were included in a multivariable model, *spa*-CC 630, *spa*-CC 084, and *spa*-CC 876 appeared to be associated with an increased risk of SSTI. However, when host and environmental covariates were included in the model and corrections were made for multiple comparisons, no *spa*-CCs were found to be significantly associated with an increased risk of SSTI. This failure to identify a link between colonisation with specific *spa*-CCs and risk of SSTI once host and environmental covariates were accounted for suggests that any difference in pathogenicity between colonising strains of *S. aureus* is likely to have a relatively trivial impact on risk of SSTI when compared with the impact of differences in the social determinants of health. Microbiological confirmation of SSTI diagnoses was not feasible and a proportion of the SSTI outcomes would be expected to have been caused by bacteria other than *S. aureus*, e.g. *Streptococcus pyogenes*. In addition, it is possible that a subset of more virulent *S. aureus* strains caused a higher proportion of SSTIs, but that the colonising isolate found on swabs was not the one that caused disease due to a switch in colonising strain.

Some of the apparent differences in risk of SSTI between strains in unadjusted analyses may have been due to confounding. We identified differences in the distribution of *spa*-CCs across ethnic groups, which in some cases mirrored ethnic disparities in risk for SSTI. For example, colonisation with *spa*-CC 876 was more common in Māori children than in children of European/Other ethnicity (RR 2.28; 95% CI 1.17 – 4.46) (**Table 41**), and colonisation with spa-CC 876 was associated with an increased incidence of SSTI (RR 2.50, 95% CI 1.27 –

4.92) (**Table 43**). Correction for multiple comparisons suggested that these differences were likely to be due to random variation but they could still act as a source of confounding.

Previous research has drawn links between carriage of virulence factors (such as genes for methicillin resistance or the Panton-Valentine leucocidin) by particular strains of *S. aureus* and an increased risk of community-onset disease (32, 33, 261), while other studies have disputed these associations (30). We used *spa*-typing and clustered strains into *spa* clonal complexes using the BURP algorithm, an approach that has been shown to closely correlate to MLST clonal complexes (147). However, it is possible that genotype as classified by *spa*-CC does not correlate adequately well with the presence of virulence factors. For example, both caMRSA and methicillin-susceptible strains were found within the same *spa*-CCs, and the greater degree of risk of SSTI seen with MRSA colonisation would suggest that additional virulence factors may well have been acquired along with methicillin resistance. In recent years the spread of caMRSA strains has been a major cause for concern in many countries, with different strains becoming predominant in different geographical regions, such as the AK3 (MLST CC 5-scc mecIV) MRSA strain in NZ and the USA300 strain in North America (115, 238, 262). In the previous chapter, MRSA colonisation was found to be associated with an increased risk of SSTI, although that was not demonstrated in the current study.

We found that MRSA comprised 21.6% of strains colonising Māori children and 19% of strains colonising Pacific children, compared with only 4.2% of strains colonising children of European/Other ethnicity. This supports the findings of a previous study conducted in NZ, which found that amongst people with culture-proven *S. aureus* infection, caMRSA was more likely to be isolated from people of Māori or Pacific ethnicity (22). The reason for this ethnic imbalance in MRSA colonisation and infection rates is not known. *Spa*-CC 002 (almost exclusively *spa*-type t002) accounted for over 80% of MRSA isolates and represents the AK3 MRSA strain, which typically does not carry the Panton-Valentine leucocidin genes *lukF-PV* and *lukS-PV* (238). This finding is consistent with the ongoing expansion of this clone observed amongst clinical isolates typed by the Institute of Environmental Science and Research (ESR), NZ's public health reference laboratory (238, 260). A smaller number of *spa*-CC 630 MRSA strains were found, largely *spa*-types t127 and t267; this *spa*-CC represents the WR/AK1 MRSA strain (MLST CC 1-IV) (260).

We found that colonisation with discordant strains of *S. aureus* across different anatomical sites was common – between 22 and 30 percent depending on which pair of sites was compared. The few previous studies on this topic have demonstrated an even higher rate of discordant-strain colonisation – Antri *et al.* and Williamson *et al.* showed *spa*-type discordance rates of 38.3% and 40.1% respectively amongst children with both anterior nares and oropharyngeal colonisation (251, 252). Studies in patients with an *S. aureus* SSTI have shown that discordance between infecting and colonising strains is also common in this setting, with a range of frequencies between 4.7 and 52 percent depending on the molecular methods used (116, 263). Our study is likely to have underestimated the prevalence of discordant-strain colonisation, firstly because some children colonised at multiple sites did not have isolates from every site available for typing, and secondly because we did not test for multiple-strain colonisation within a single anatomical site as only a single colony was chosen for genotyping. However, previous studies suggest that multiple-strain colonisation within a single site, e.g. the anterior nares, is relatively uncommon (220, 250). We found that discordant-strain colonisation was associated with an increased risk of SSTI in unadjusted analyses, but not once covariates were accounted for. It is possible that discordant-strain colonisation across different anatomical sites as observed in this study could be stable over time, or it could be a marker of frequent exposure to new strains or recent acquisition of a new strain with turnover in progress; both the latter scenarios might be associated with a time of increased risk of SSTI.

The strengths of this study include the size, and the ethnic and socioeconomic diversity of the *Growing Up in New Zealand* cohort. This study does however, have a number of limitations, primarily that not all *S. aureus* isolates were available for genotyping. Thus, colonised children without a stored isolate could not be included, significantly reducing the sample size. Nevertheless, the study sample still constituted a large group of children. The outcome used in this study was a composite of parent-reported and hospitalised SSTI. Little instruction was given to parents regarding SSTI diagnosis, so over-diagnosis and uncertainty about the difference between SSTI and eczema may also have affected the results.

In conclusion, this study does not support a link between colonising *S. aureus* genotype and risk of SSTI. While some associations between *spa*-CCs and risk of SSTI were found on unadjusted analyses, these were not confirmed in multivariable models, demonstrating the importance of correcting for covariates such as ethnicity and eczema, and for multiple comparisons. This study identified variation in the distribution of genotypes across ethnicities – a potential source of confounding. Multiple strain colonisation was found to be common amongst children colonised at more than one site. Further research is required to better understand the dynamics of *S. aureus* colonisation both within and across multiple anatomical sites, particularly in children. Overall, the findings of this study would suggest that interventional studies aiming to reduce the risk of SSTI should focus on addressing imbalances in the social determinants of health, and possibly the eradication of *S. aureus* colonisation for high risk children, and not on attempting to identify and replace or eradicate specific high-risk strains of *S. aureus* (35, 228, 264).

9.5 TABLES

Table 38: Demographic and environmental factors amongst *Staphylococcus aureus* colonised children with and without a stored isolate of *S. aureus* available for genotype testing.

Explanatory variable	***S. aureus* isolate status, n (%)**		**P-value**
	Not available	**Available**	
Total	935 (100)	1332 (100)	
Male sex	480 (51.3)	698 (52.4)	0.62
Ethnicity			
European/Other	573 (61.3)	837 (62.8)	0.02
Māori	100 (10.7)	176 (13.2)	
Pacific	140 (15.0)	195 (14.6)	
Asian	122 (13.1)	124 (9.3)	
Presence of eczema	235 (25.1)	384 (28.8)	0.05
Socioeconomic deprivation	222 (23.7)	360 (27.0)	0.08
Household crowding	181 (19.4)	233 (17.5)	0.25
SSTI outcome	122 (13.1)	184 (13.8)	0.60

Table 39: Number and percentage of 1332 children colonised with *Staphylococcus aureus* by site of colonisation and *spa* clonal complex (*spa*-CC) of isolate, for clonal complexes colonising ≥10 children at any site.

***spa*-CC**	**Number of children colonised by anatomical site, n (%)**			
	Any site [a]	**Anterior nares**	**Oropharynx**	**Antecubital fossa**
Total	1332 (100)	781 (100)	759 (100)	166 (100)
CC 630	492 (36.9)	267 (34.29)	275 (36.2)	57 (34.3)
CC 002	417 (31.3)	223 (28.6)	226 (29.8)	61 (36.8)
CC 275	85 (6.4)	58 (7.4)	36 (4.7)	6 (3.6)
CC 121/304	78 (5.9)	39 (5.0)	43 (5.7)	6 (3.6)
CC 084	71 (5.3)	28 (3.6)	50 (6.6)	11 (6.6)
CC 876	46 (3.5)	31 (4.0)	22 (2.9)	4 (2.4)
CC 216	29 (2.2)	14 (1.8)	16 (2.1)	5 (3.0)
CC 089	24 (1.8)	22 (2.8)	7 (0.9)	1 (0.6)
CC 8317/148	13 (1.0)	6 (0.8)	9 (1.2)	1 (0.6)
CC 364	12 (0.9)	11 (1.4)	1 (0.1)	0
Other [b]	147 (11.0)	82 (10.5)	74 (9.8)	14 (8.5)

Table 39 footnote: [a] 'any site' refers to the number of children colonised with the respective *spa*-CC at one or more sites; due to discordant-strain colonisation across anatomical sites, the sum of this column is greater than the number of children in the study. [b] 'Other' includes less frequent spa-CCs, singletons, non-typable isolates, and *spa*-types excluded from clustering due to short repeat sequences.

Table 40: Number and percentage of 1332 children colonised with *Staphylococcus aureus* by site of colonisation and s*pa*-type, for *spa*-types with a frequency ≥10 children

Anterior nares		**Oropharynx**		**Antecubital fossa**	
***spa*-type**	**n (%)**	***spa*-type**	**n (%)**	***spa*-type**	**n (%)**
t002	85 (10.88)	t002	78 (10.32)	t002	27 (16.77)
t189	62 (7.94)	t189	72 (9.52)	t127	18 (11.18)
t127	59 (7.55)	t1265	59 (7.8)	t189	12 (7.45)
t1265	53 (6.79)	t127	57 (7.54)	t1265	10 (6.21)
t015	25 (3.2)	t084	25 (3.31)		
t179	21 (2.69)	t267	19 (2.51)		
t267	15 (1.92)	t015	16 (2.12)		
t084	13 (1.66)	t701	14 (1.85)		
t359	13 (1.66)	t179	13 (1.72)		
t012	12 (1.54)	t216	12 (1.59)		
t065	11 (1.41)	t359	12 (1.59)		
t089	11 (1.41)				
t701	11 (1.41)				
t216	10 (1.28)				

Table 41: Unadjusted relative risks (95% CI) for colonisation with *S. aureus* from the six most common *spa*-CCs, by demographic and environmental covariate exposure.

Exposure variable	***spa*-CC 630**	***spa*-CC 002**	***spa*-CC 275**	***spa*-CC 121/304**	***spa*-CC 084**	***spa*-CC 876**	**Multiple strains**
Male sex	1.05 (0.91 – 1.21)	0.89 (0.76 – 1.04)	1.02 (0.68 – 1.54)	1.24 (0.80 – 1.92)	1.17 (0.74 – 1.85)	1.55 (0.86 – 2.79)	1.24 (0.80 – 1.92)
Ethnicity							
European/Other	Reference	Reference	Reference	Reference	Reference	Reference	
Māori	1.07 (0.87 – 1.32)	1.21 (0.97 – 1.51)	0.43 (0.19 – 0.98)	1.03 (0.55 – 1.93)	0.76 (0.35 – 1.65)	2.28 (1.17 – 4.46)	1.81 (1.04 – 3.15)
Pacific	1.07 (0.88 – 1.31)	1.20 (0.97 – 1.48)	0.46 (0.21 – 0.98)	1.09 (0.61 – 1.97)	0.88 (0.44 – 1.77)	1.03 (0.43 – 2.48)	1.33 (0.73 – 2.43)
Asian	1.08 (0.85 – 1.37)	0.86 (0.63 – 1.18)	0.61 (0.27 – 1.39)	0.40 (0.13 – 1.25)	1.69 (0.90 – 3.18)	0.81 (0.25 – 2.64)	1.13 (0.52 – 2.45)
Presence of eczema	1.14 (0.98 – 1.32)	1.03 (0.87 – 1.23)	0.66 (0.40 – 1.10)	1.03 (0.64 – 1.66)	0.61 (0.34 – 1.07)	1.45 (0.80 – 2.60)	1.03 (0.64 – 1.66)
Socioeconomic deprivation	1.01 (0.86 – 1.18)	1.22 (1.03 – 1.45)	0.63 (0.37 – 1.06)	0.87 (0.53 – 1.44)	0.99 (0.59 – 1.65)	1.44 (0.79 – 2.61)	1.20 (0.75 – 1.91)
Household crowding	1.16 (0.98 – 1.37)	1.09 (0.89 – 1.33)	0.49 (0.24 – 1.00)	1.03 (0.59 – 1.81)	0.77 (0.40 – 1.49)	1.31 (0.66 – 2.60)	1.31 (0.78 – 2.21)

Table 41 Footnote: None of these associations between specific *spa*-CCs and the exposure variables were significant after correction for multiple comparisons with the Benjamini-Hochberg procedure specifying a false discovery rate of up to 10%. This procedure was not applied to associations for multiple strains for which the association with Māori ethnicity was significant with a p-value of 0.03.

Table 42: Number and percentage of 117 children colonised with methicillin–resistant *Staphylococcus aureus* (MRSA) by site of colonisation and *spa* clonal complex (*spa*–CC) of isolate.

***spa*–CC**	**Any site, n (%)[a]**	**Anterior nares, n (%)**	**Oropharynx, n (%)**	**Antecubital fossa, n (%)**
Total	117 (100)	72 (100)	62 (100)	26 (100)
CC 002	97 (82.9)	59 (81.9)	51 (82.3)	21 (80.8)
CC 630	11 (9.4)	<10 (9.7)	<10 (11.3)	<10 (7.7)
Other CC	11 (9.4)	<10 (8.3)	<10 (6.5)	<10 (11.5)

Table 42 footnote: Frequency of colonisation at any site adds up to more than 100% as children could be colonised with discordant strains of MRSA at different sites.

Table 43: Associations between colonisation at any site (nose, throat, or skin) with various *spa* clonal complexes (*spa*-CC) of *Staphylococcus aureus*, and demographic and environmental covariates, and skin or soft tissue infection in the year prior to bacterial sampling.

Variable	**Total, n (%)**	**SSTI outcome**		**Unadjusted**		**Multivariable, *spa*–CCs only**		**Multivariable, with covariates**	
		Yes, n (%)	**No, n (%)**	**RR (95% CI)**	**p–value**	**RR (95% CI)**	**p–value**	**RR (95% CI)**	**p–value**
Total	1332 (100)	184 (13.8)	1148 (86.2)						
spa-CC [a]									
CC 630	492 (36.9)	78 (15.9)	414 (84.2)	1.66 (1.02 – 2.69)	0.04	1.69 (1.14 – 2.50)	0.009 *	1.32 (0.88 – 2.08)	0.20
CC 002	417 (31.3)	59 (14.2)	358 (85.9)	1.48 (0.90 – 2.43)	0.12	1.47 (0.98 – 2.17)	0.06 *	1.03 (0.66 – 1.66)	0.91
CC 275	85 (6.4)	7 (8.2)	78 (91.8)	0.86 (0.37 – 1.98)	0.72	0.86 (0.36 – 1.74)	0.7	0.81 (0.33 – 1.69)	0.60
CC 121/304	78 (5.9)	9 (11.5)	69 (88.5)	1.21 (0.57 – 2.57)	0.63	1.17 (0.55 – 2.21)	0.65	0.87 (0.40 – 1.70)	0.70
CC 084	71 (5.3)	13 (18.3)	58 (81.7)	1.91 (0.99 – 3.70)	0.05	1.91 (1.02 – 3.28)	0.03 *	1.85 (0.97 – 3.35)	0.05
CC 876	46 (3.5)	11 (23.9)	35 (76.1)	2.50 (1.27 – 4.92)	0.008 *	2.44 (1.27 – 4.17)	0.003 *	1.51 (0.77 – 2.77)	0.20
Residual group [b]	188 (14.1)	18 (9.6)	170 (90.4)	Reference		Reference			
MRSA colonisation	120 (9.0)	27 (22.5)	93 (77.5)	1.74 (1.21 – 2.50)	0.004			1.34 (0.87 – 1.99)	0.17
Discordant strain colonisation [c]	78 (5.9)	17 (21.0)	64 (79.0)	1.57 (1.01 – 2.45)	0.05			1.09 (0.60 – 1.83)	0.76

Table 43 continued	**Total, n (%)**	**SSTI outcome**		**Unadjusted**		**Multivariable, *spa*–CCs only**		**Multivariable, with covariates**	
Variable		**Yes, n (%)**	**No, n (%)**	**RR (95% CI)**	**p–value**	**RR (95% CI)**	**p–value**	**RR (95% CI)**	**p–value**
Male sex	698 (52.4)	103 (14.8)	595 (85.2)	1.16 (0.88 – 1.51)	0.30			1.04 (0.80 – 1.36)	0.77
Ethnicity									
European/Other	837 (62.8)	93 (11.1)	744 (88.9)	Reference				Reference	
Māori	176 (13.2)	43 (24.4)	133 (75.6)	2.20 (1.59 – 3.04)	<0.0001			1.69 (1.18 – 2.38)	0.004
Pacific	195 (14.6)	41 (21.0)	154 (79.0)	1.89 (1.36 – 2.64)	0.0002			1.48 (1.01 – 2.14)	0.04
Asian	124 (9.3)	7 (5.7)	117 (94.4)	0.51 (0.24 – 1.07)	0.06			0.46 (0.20 – 0.89)	0.04
Presence of eczema	384 (28.8)	80 (20.8)	304 (79.2)	1.90 (1.46 – 2.48)	<0.0001			1.83 (1.41 – 2.38)	<0.0001
Socioeconomic deprivation	360 (27.0)	72 (20.0)	288 (80.0)	1.74 (1.33 – 2.27)	<0.0001			1.30 (0.97 – 1.74)	0.07
Household crowding	233 (17.5)	46 (19.7)	187 (80.3)	1.57 (1.16 – 2.13)	0.004			1.12 (0.80 – 1.54)	0.50

Table 43 footnote: For *spa*-CCs only, p-values which were significant after the Benjamimi-Hochberg procedure are marked with a '*'. [a] The *spa*-CC variables overlap as 45 children were colonised with *S. aureus* of differing *spa*-CCs at differing anatomical sites. [b] The 'residual group' refers to a group of children colonised with heterogeneous *S. aureus* strains without overlap with the other *spa*-CCs. These children were colonised with *S. aureus* from less frequent *spa*–CCs, singletons, excluded *spa*-types, or non-typable isolates, but not by *S. aureus* from one of the six specified *spa*-CCs. [c] 'Discordant strain colonisation' refers to children colonised with *S. aureus* at more than one site, with different *spa*-CCs isolated from different sites.

CHAPTER 10: *STREPTOCOCCUS PYOGENES* COLONISATION, *STAPHYLOCOCCUS AUREUS* CO-COLONISATION, AND RISK OF SKIN AND SOFT TISSUE INFECTION IN PRESCHOOL AGE CHILDREN

Chapters 7, 8, and 9 have respectively looked at associations between the risk of SSTI and colonisation with *Staphylococcus aureus* in general, colonisation with an MRSA strain of *S. aureus*, and colonisation with particular genotypes (*spa*-types) of *S. aureus*. *S. aureus* colonisation in general, and MRSA colonisation in particular, were associated with small increases in the risk of SSTI, but the genotype of the colonising strain did not appear to alter the risk significantly.

Compared with *S. aureus*, the asymptomatic carrier state for *Streptococcus pyogenes* is less well defined. *S. pyogenes* carriage is most commonly identified in people presenting with recurrent pharyngitis who are found to be repeatedly throat swab culture-positive for *S. pyogenes* but anti-streptococcal antibody negative. Whether *S. pyogenes* oropharyngeal carriage increases the risk of recurrent pharyngitis or of distant infections such as SSTI is not clear. These are important questions because compared with similar developed nations, the burden of SSTI in NZ children is high, as is the burden of acute rheumatic fever which is generally recognised to be due to recurrent streptococcal pharyngitis.

This chapter looked at associations between colonisation with *S. pyogenes*, co-colonisation with *S. aureus*, and risk of SSTI. *S. pyogenes* was largely detected on oropharyngeal swabs and was rare at the other swab sites. Māori and Pacific children were more likely to be colonised with *S. pyogenes* in unadjusted analyses but not in multivariable analyses, while Asian children were less likely to be colonised with *S. pyogenes* in both analyses. Similarly, Māori children were more likely, and Asian children less likely, to be co-colonised with both *S. pyogenes* and *S. aureus*. *S. pyogenes* colonisation was strongly associated with an increased risk of SSTI. However, when co-colonisation with both *S. pyogenes* and *S. aureus* was considered, co-colonisation was associated with an increased risk of SSTI while colonisation with either *S. pyogenes* or *S. aureus* alone was not. It remains unclear whether these associations between *S. pyogenes* colonisation and SSTI, and co-colonisation and SSTI, are due to direct causative effects, perhaps due to an increased propensity to develop streptococcal SSTIs such as impetigo and cellulitis, or whether there are underlying factors that predispose both to *S. pyogenes* colonisation and to SSTI.

10.1 INTRODUCTION

New Zealand (NZ) children suffer from high rates of skin and soft tissue infection (SSTI), with Māori and Pacific children and children living in socioeconomic deprivation the worst affected (57, 265). *Streptococcus pyogenes* and *Staphylococcus aureus* are the most commonly identified bacterial pathogens in patients with SSTI, and empiric treatment is directed at these organisms. Persistent nasal colonisation with *S. aureus* is associated with an increased risk of nosocomial *S. aureus* infection (25), and both our previous research and that of others has shown that colonisation with *S. aureus* is also associated with an increased risk of community-onset SSTI (249, 266). To our knowledge, there are no previous studies that have shown whether *S. pyogenes* colonisation is also associated with an increased risk of SSTI.

The dynamics of the carrier state for *S. pyogenes*, which is detected in the oropharynx in about 10% of healthy people, are not as well defined as those of the carrier state for *S. aureus* (267, 268). It has been suggested that carriage can be differentiated from infection by the lack of a serological response to *S. pyogenes*. However, serology is seldom used in uncomplicated streptococcal infection, a lack of serological response is common (269), and serological response does not appear to determine response to antibiotic therapy (270). Almost all school-aged children appear to be susceptible to acquiring *S. pyogenes* in the oropharynx; in a longitudinal study of school children in the United States, Cornfeld and Hubbard found that over 90% of children had *S. pyogenes* isolated on one or more occasions during 4 years of follow-up (271). In a more recent study, Martin *et al.* showed that over any single year of follow-up approximately 30% of children acquired *S. pyogenes* carriage detected on ≥2 sequential throat swabs over ≥1 week, while another 30% of children had ≥1 episodes of acquisition detected on a single throat swab (272). In both carriers and those with single episodes, around half of new acquisitions were associated with typical symptoms of pharyngitis. Carriers were also noted to occasionally develop symptoms when their colonising *emm*-type changed. The mean duration of carriage was 10.8 weeks and the maximum duration of carriage detected was 127 weeks. It is plausible that long-term colonisation of the oropharynx could act as a source for *S. pyogenes* SSTI.

Growing Up in New Zealand is a large and diverse longitudinal birth cohort study with access to data from parental interviews, linked national administrative health datasets, and the results of culture for *S. aureus* and *S. pyogenes* from swabs routinely collected from the nose, throat and skin of participating children at 4½ years of age. Data on SSTI outcomes are available from linked hospitalisation records and from parental report. The objectives of this study were to use these data to: determine the prevalence and predictors of *S. pyogenes* colonisation in NZ children; to look for associations between *S. pyogenes* colonisation and SSTI while controlling for demographic and environmental covariates; to determine the prevalence and predictors of *S. aureus* and *S. pyogenes* co-colonisation; and to look for associations between co-colonisation with both organisms and SSTI.

10.2 METHODS

10.2.1 Ethics

Ethical approval was obtained from the Ministry of Health Northern Y Regional Ethics Committee (NTY/08106/055). Specific written informed consent was obtained from each child's primary caregiver for microbiological sampling and for linkage with administrative health data.

10.2.2 Study sample

This study was performed within the *Growing Up in New Zealand* longitudinal birth cohort. The cohort consists of 6583 children born in 2009 and 2010 whose mothers were enrolled during the antenatal period. The cohort is generalizable to the national birth cohort with regards to socioeconomic status and ethnicity. Enrolment, retention and generalizability have been described elsewhere (37-39). Face-to-face interviews with the primary caregivers of the cohort children were conducted in the antenatal period, and at 9 months, and 2 and 4½ years of child age.

10.2.3 Microbiological methods

At the interview conducted at 4½ years of child age, interviewers used Copan eSwabs (Brescia, Italy) to sample the anterior nares, oropharynx, and antecubital fossa skin of participating children. Culture was performed at a single community medical laboratory in Auckland, NZ. The swabs from the anterior nares and antecubital fossa samples were inoculated onto tryptic soy sheep blood agar and those from the oropharynx onto 3% salt Columbia sheep blood agar. The agar plates were then incubated for 48 hours at 35°C in 5% CO2. Suspected colonies of *S. pyogenes* or *S. aureus* were identified using matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry (BD Bruker Biotyper, Franklin Lakes, New Jersey, U.S.A.). Isolates were stored at -80°C in Protect TS/80 Cryovials with Micro-organism Preservation Beads (Technical Service Consultants, Heywood, United Kingdom).

To perform e*mm*-typing, stored isolates were inoculated onto sheep blood agar and incubated for 24 hours at 37°C. Colonies were picked from the agar plate and directly added to the PCR master mix in 96-well PCR plates (273), with a 5-minute preheating step at 95°C added to the PCR programme (274). Standard *emm*-typing forward (5'-TATTSGCTTAGAAAATTAA) and reverse (5'-GCAAGTTCTTCAGCTTGTTT) primers were used (Sigma-Aldrich, St. Louis, MO, USA). Sequencing of the amplified DNA was performed by Macrogen Inc. (Seoul, Korea). Consensus sequences were constructed using Geneious software (Biomatters Limited, Auckland, NZ). The *emm*-type was determined by entering the nucleotide sequence into the National Center for Biotechnology Information Basic Local Alignment Search Tool (BLAST) (275). Selected *emm*-types were confirmed by alignment with reference sequences (276).

10.2.4 Variables

Explanatory variables were obtained from the interview conducted with each child's primary caregiver at 4½ years of child age, and included the child's sex and ethnicity, parental report of eczema, socioeconomic deprivation, and household crowding. The selection of these variables was informed by previous research on SSTI in the cohort. The child's ethnicity was defined as the primary ethnic group the child identified with as provided by their primary caregiver. Responses were aggregated into broad groups – Māori, Pacific, Asian, and a

residual European/Other group. The presence of eczema was based on parental report of eczema in the preceding year. The presence of socioeconomic deprivation was determined using the NZiDep index (50), calculated from the responses to questionnaire items by the primary caregiver, with socioeconomic deprivation defined as an NZiDep score of 3 or more. The presence of household crowding was defined as a ratio of occupants to bedrooms of 2 or more.

The primary outcome for the colonisation part of the study was isolation of *S. pyogenes* from ≥1 of the three sites swabbed – the anterior nares, oropharynx, or antecubital fossa skin. More extensive data on *S. aureus* colonisation has been presented previously (249), but isolation of *S. aureus* from ≥1 of the three sites has been included as a secondary outcome in this study to allow for the description of co-colonisation. Co-colonisation with *S. pyogenes* and *S. aureus* was defined as isolation of both organisms from a participant, regardless of whether they were isolated from the same or different sites (e.g. *S. pyogenes* from the oropharynx and *S. aureus* from the anterior nares). Conversely, sole colonisation was defined as isolation of either *S. pyogenes* or *S. aureus* alone from a participant.

The outcome of the SSTI part of the study was a composite of parental report of SSTI and/or hospitalisation for an SSTI, both in the year prior to the 4½ year interview and treated as a binary categorical variable. Hospitalisations for an SSTI were identified using the National Minimum Dataset, an administrative record of all public hospital discharges. All acute paediatric care is provided through public hospitals in NZ. The first ICD-10 diagnostic code was used to identify admissions for which SSTI was the main contributor.

10.2.5 Statistical analyses

Analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC, USA). Unadjusted analyses were presented using relative risks, 95% confidence intervals and p-values from the χ^2 or Fisher's exact tests. As SSTI was not a rare outcome, multivariable analyses were conducted using log-binomial regression to directly calculate adjusted relative risks, confidence intervals and p-values.

10.3 RESULTS

10.3.1 Prevalence and predictors of S. pyogenes colonisation

Complete data from the 4½ year interview, the linked National Minimum Dataset, and the bacterial swab results were available for 5235/6583 (80%) children in the GUINZ cohort. Of these 5235 children, 524 (10.1%) were colonised with *S. pyogenes* at one or more of the three sites – 69/5235 (1.3%) in the nose, 504/5235 (9.6%) in the throat, and 15/5235 (0.3%) on the skin. Of those colonised in the throat, 52/504 (10.3%) were also colonised in the nose, and 11/504 (2.2%) were also colonised on the skin.

There was a highly significant negative association between *S. pyogenes* colonisation and Asian ethnicity in both unadjusted and multivariable analyses (**Table 44**). There were significant positive associations between *S. pyogenes* colonisation and Māori or Pacific ethnicity in the unadjusted analysis but these associations were not statistically significant after adjustment for covariates in the multivariable analysis. Sex, eczema, socioeconomic deprivation, and household crowding were not associated with *S. pyogenes* colonisation.

10.3.2 Associations between S. pyogenes colonisation and SSTI

A total of 643/5235 (12.3%) children experienced an SSTI in the year prior to the interview conducted at 4½ years of child age, including 35/5235 (0.7%) who had one or more hospital admissions for an SSTI during this time period. There was a significant positive association between *S. pyogenes* colonisation and a history of SSTI in the preceding year – an SSTI had occurred in 17.4% of those colonised with *S. pyogenes*, compared with 11.7% of those not colonised with *S. pyogenes* (aRR 1.38, 95% CI 1.13 – 1.68, p=0.001) (**Table 45**).

There were also significant positive associations between a history of an SSTI and Māori or Pacific ethnicity in both the unadjusted and multivariable analyses. In contrast, there was a significant negative association between a history of an SSTI and Asian ethnicity in both the unadjusted and multivariable analyses. There were significant positive associations between a

history of an SSTI and a history of eczema or household crowding in both the unadjusted and multivariable analyses. Socioeconomic deprivation was associated with a history of an SSTI in the unadjusted analysis but not in the multivariable analysis.

10.3.3 Prevalence and predictors of S. aureus and S. pyogenes co-colonisation, and associations between co-colonisation and SSTI

Of the 5235 children included in this study, 2267 (43.3%) were colonised with *S. aureus* at one or more sites, including 1399/5235 (26.7%) who were colonised with *S. aureus* in the oropharynx. Of the 524 children who were colonised with *S. pyogenes*, 240/524 (45.8%) were co-colonised with *S. aureus*, including 129/504 (25.6%) who were colonised with both *S. pyogenes* and *S. aureus* in the oropharynx. Colonisation with *S. aureus* was not associated with colonisation with *S. pyogenes*, either at any site (p=0.22) or in the oropharynx (p=0.55).

There was a significant positive association between *S. pyogenes* and *S. aureus* co-colonisation and Māori ethnicity, and a significant negative association between *S. pyogenes* and *S. aureus* co-colonisation and Asian ethnicity, in both unadjusted and multivariable analyses (**Table 46**). Sex, eczema, socioeconomic deprivation, and household crowding were not significantly associated with *S. pyogenes* and *S. aureus* co-colonisation.

There was a strong positive association between a history of an SSTI and co-colonisation with both *S. aureus* and *S. pyogenes* (aRR 1.74, 95% CI 1.17 – 2.64, p=0.008) (**Table 47**). In contrast, there were no significant associations between a history of an SSTI and either *S. pyogenes* sole colonisation, or *S. aureus* sole colonisation, in both the unadjusted and multivariable analyses.

10.3.4 Results of emm-typing

S. pyogenes isolates were available for genotyping for 189/524 (36.1%) colonised children. An *emm*-type was able to be assigned for isolates from 151/189 (79.9%) children. The most common *emm*-types observed were *emm*12 (n=35, 23.2%), *emm*89 (n=27, 17.9%), and *emm*1

(n=26, 17.2%). None of these predominant *emm*-types were significantly associated with history of an SSTI in unadjusted analyses so multivariable analyses were not attempted.

10.4 DISCUSSION

This study, conducted in a large and diverse cohort of NZ children, has demonstrated a number of important findings about the relationship between *S. pyogenes* colonisation and SSTI. *S. pyogenes* colonisation at 4½ years of age was strongly associated with a history of an SSTI in the preceding year. We have previously identified a similar relationship between *S. aureus* colonisation at 4½ years and history of an SSTI in the preceding year (249). In addition, the current study has shown that the increased risk of SSTI associated with colonisation with *S. pyogenes* and *S. aureus* occurred largely in those children who were co-colonised with both organisms.

Colonisation with *S. pyogenes* was common with a prevalence of 10.1%; this is consistent with previous studies that have found *S. pyogenes* colonisation of the throat in 10-15% of healthy people (267, 268, 277). Studies conducted in sore throat programmes and in family medicine practices tend to isolate *S. pyogenes* from the throat at a higher frequency – up to 40% in some cases – as they select for people with symptomatic streptococcal pharyngitis (269). The *emm*-types we identified were also commonly found in previous NZ studies using throat swab isolates from a community medical laboratory (278), and invasive isolates from a national reference laboratory (279).

Previous studies of *S. pyogenes* oropharyngeal colonisation have investigated the relationship between colonisation and acute pharyngitis (269, 272). We are not aware of any population level studies which have demonstrated an association between *S. pyogenes* oropharyngeal colonisation and SSTI. However, there is indirect evidence that supports an association between *S. pyogenes* colonisation and SSTI: firstly, *S. pyogenes* skin colonisation has been shown to precede skin infection at sites of minor trauma (280); and secondly, *S. pyogenes* oropharyngeal colonisation has been epidemiologically linked with cases of invasive infection

(e.g. streptococcal toxic shock syndrome) in contacts (281). In contrast, a study in tropical northern Australia found a low prevalence (3.7%) of pharyngeal colonisation in Aboriginal children with a high incidence of SSTI (20). The authors interpreted this finding as supporting a hypothesis that recurrent SSTI had an immunising effect that was protective against oropharyngeal colonisation. In addition, it has been suggested that the strains of *S. pyogenes* that cause SSTI differ from those that cause oropharyngeal infection (282). Our results are therefore likely to be generalizable to other temperate countries but may not apply in tropical areas.

In unadjusted analyses we found marked ethnic differences in the prevalence of *S. pyogenes* colonisation, with the highest prevalence seen in Pacific and Māori children, and the lowest in Asian children. These differences mirrored the ethnic disparities in the incidence of SSTI, supporting the hypothesis that *S. pyogenes* colonisation increased the risk of SSTI, and suggesting that differences in *S. pyogenes* colonisation rates could have contributed to the ethnic disparities in SSTI rates. In adjusted analyses, the increased risk of *S. pyogenes* colonisation in Māori and Pacific children was not significant when socioeconomic deprivation and household crowding were accounted for, while the increased risk of SSTI persisted. In contrast, we found that in Asian children both the reduced risk of *S. pyogenes* colonisation and of SSTI persisted after accounting for socioeconomic deprivation and household crowding. These findings suggest the need for further research to identify unmeasured factors in the household environment that may contribute to the marked variation between people in the prevalence of *S. pyogenes* colonisation and the incidence of SSTI (127, 129, 131).

This study is the first to demonstrate a strong association between co-colonisation with *S. pyogenes* and *S. aureus* and SSTI. We found that in adjusted analyses only co-colonisation, and not colonisation with either organism alone was associated with an increased risk of SSTI. While previous studies have demonstrated that pharyngeal co-colonisation is common (277), to our knowledge no previous studies have demonstrated an association between co-colonisation and risk of SSTI. Co-colonisation in this study was not confined solely to the oropharyngeal site – while *S. pyogenes* colonisation was predominantly oropharyngeal, in 46% of cases the co-colonising *S. aureus* was detected elsewhere. The observation that both organisms can be readily recovered as co-pathogens from infected skin lesions supports the

plausibility of a causal relationship between co-colonisation and SSTI (29). Socioeconomic deprivation and household crowding were not associated with co-colonisation in this study. This was surprising as crowding in particular would have been expected to have offered more frequent opportunities to have encountered both organisms. There are several reasons that this novel finding is important: firstly, the role of co-colonisation needs to be considered in future studies investigating links between infection and colonisation with either organism alone; and secondly, the population of children who are co-colonised with both organisms is relatively small and easy to identify, so they could be targeted as a high risk group in interventional trials aiming to reduce their risk of SSTI.

Strengths of this study include the large size and diversity of the cohort, and the high rates of retention and of consent to biological sampling and linkage to administrative data. This study also has some limitations. The bacterial swabs were collected at a single time point which did not provide information about the duration or dynamics of colonisation. Symptom status at the time of collection was not obtained. While we have assumed that most colonisation was asymptomatic, pharyngitis is common in children so some may have had sore throats at the time of sampling. SSTI diagnosis was largely by parental report. Brief instructions were provided to parents but misdiagnosis and incomplete recall may have affected results. Isolates were not available for genotyping for a majority of the *S. pyogenes* colonised children, limiting our ability to describe circulating *emm*-types.

This study has demonstrated important novel findings regarding the relationships between *S. pyogenes* colonisation, *S. aureus* co-colonisation, and risk of SSTI. Colonisation with *S. pyogenes* was less common in Asian children, and appeared more common in Māori and Pacific children until environmental differences were also considered. While *S. pyogenes* colonisation was associated with a higher risk of SSTI, when co-colonisation with both *S. pyogenes* and *S. aureus* was accounted for, colonisation with either organism alone was no longer associated with an increased risk of SSTI. These findings need to be confirmed by prospective studies to better define the temporal relationships between acquisition of colonisation and onset of infection. Such a study would ideally include frequent repeated sampling from multiple sites and microbiological confirmation of incident SSTIs. If proven, children with co-colonisation would constitute a defined group for whom interventions to

reduce the burden of bacterial colonisation could be targeted, with the aim of reducing the high rates of SSTI seen in NZ and comparable developed countries.

10.5 TABLES

Table 44: Unadjusted and multivariable log-binomial adjusted associations between *Streptococcus pyogenes* colonisation, and demographic and environmental explanatory variables.

Explanatory variable	**Total, n (%)**	***S. pyogenes* colonisation, n (%)**		**Unadjusted analyses**		**Multivariable analyses**	
		Present	**Absent**	**RR (95% CI)**	**P-value**	**aRR (95% CI)**	**P-value**
Total	5235 (100.0)	524 (10.0)	4711 (90.0)				
Male sex	2690 (51.4)	277 (10.3)	2413 (89.7)	1.06 (0.90 – 1.25)	0.48	1.06 (0.90 – 1.24)	0.50
Ethnicity							
European/Other	3229 (61.7)	320 (9.9)	2909 (90.1)	Reference		Reference	
Māori	634 (12.1)	81 (12.8)	553 (87.2)	1.29 (1.03 – 1.62)	0.03	1.27 (0.99 – 1.60)	0.05
Pacific	764 (14.6)	96 (12.6)	668 (87.4)	1.27 (1.02 – 1.57)	0.03	1.22 (0.95 – 1.55)	0.10
Asian	608 (11.6)	27 (4.4)	581 (95.6)	0.45 (0.31 – 0.66)	<0.0001	0.44 (0.29 – 0.63)	<0.0001
Presence of eczema	1198 (22.9)	120 (10)	1078 (90)	1.00 (0.83 – 1.21)	0.99	1.00 (0.82 – 1 21)	0.99
NZiDep ≥3	1270 (24.3)	138 (10.9)	1132 (89.1)	1.12 (0.93 – 1.34)	0.24	0.97 (0.79 – 1.17)	0.74
Household crowding	951 (18.2)	108 (11.4)	843 (88.6)	1.17 (0.96 – 1.43)	0.13	1.12 (0.89 – 1.39)	0.34

Table 44 footnote: Sampled anatomical sites were the anterior nares, oropharynx, and antecubital fossa. Colonisation refers to isolation of *S. pyogenes* from any of these sites. The NZiDep is an individualised measure of deprivation derived from questionnaire responses.

Table 45: Unadjusted and multivariable log-binomial adjusted associations between skin and soft tissue infection (SSTI) and *Streptococcus pyogenes* colonisation at any site (anterior nares, oropharynx, antecubital fossa), and demographic and environmental explanatory variables.

Explanatory variable	**Total, n (%)**	**SSTI diagnosis, n (%)**		**Unadjusted analyses**		**Multivariable analyses**	
		Yes	**No**	**RR (95% CI)**	**P-value**	**aRR (95% CI)**	**P-value**
Total	5235 (100.0)	643 (12.3)	4592 (87.7)				
S. pyogenes colonisation	524 (10.0)	91 (17.4)	433 (82.6)	1.48 (1.21 – 1.81)	0.0002	1.38 (1.13 – 1.68)	0.001
Male sex	2690 (51.4)	347 (12.9)	2343 (87.1)	1.11 (0.96 – 1.28)	0.16	1.10 (0.96 – 1.27)	0.18
Ethnicity							
European/Other	3229 (61.7)	327 (10.1)	2902 (89.9)	Reference		Reference	
Māori	634 (12.1)	128 (20.2)	506 (79.8)	1.99 (1.66 – 2.40)	<0.0001	1.73 (1.42 – 2.09)	<0.0001
Pacific	764 (14.6)	145 (19)	619 (81)	1.87 (1.57 – 2.24)	<0.0001	1.53 (1.25 – 1.86)	<0.0001
Asian	608 (11.6)	43 (7.1)	565 (92.9)	0.70 (0.51 – 0.95)	0.02	0.66 (0.48 – 0.88)	0.008
Presence of eczema	1198 (22.9)	213 (17.8)	985 (82.2)	1.67 (1.44 – 1.94)	<0.0001	1.64 (1.41 – 1.90)	<0.0001
NZiDep ≥3	1270 (24.3)	211 (16.6)	1059 (83.4)	1.52 (1.31 – 1.78)	<0.0001	1.17 (0.99 – 1.37)	0.06
Household crowding	951 (18.2)	171 (18)	780 (82)	1.63 (1.39 – 1.92)	<0.0001	1.30 (1.08 – 1.55)	0.004

Table 45 footnote: Sampled anatomical sites were the anterior nares, oropharynx, and antecubital fossa. Colonisation refers to isolation of *S. pyogenes* from any of these sites. The NZiDep is an individualised measure of deprivation derived from questionnaire responses.

Table 46: Unadjusted and multivariable log-binomial adjusted associations between *Streptococcus pyogenes* and *Staphylococcus aureus* co-colonisation, and demographic and environmental explanatory variables.

Explanatory variable	**Total, n (%)**	***S. pyogenes* + *S. aureus* co-colonisation, n (%)**		**Unadjusted analyses**		**Multivariable analyses**	
		Present	**Absent**	**RR (95% CI)**	**P-value**	**aRR (95% CI)**	**P-value**
Total	5235 (100.0)	240 (4.6)	4995 (95.4)				
Male sex	2690 (51.4)	134 (5.0)	2556 (95.0)	1.20 (0.93 – 1.53)	0.16	1.19 (0.93 – 1.53)	0.16
Ethnicity							
European/Other	3229 (61.7)	140 (4.3)	3089 (95.7)	Reference		Reference	
Māori	634 (12.1)	42 (6.6)	592 (93.4)	1.53 (1.09 – 2.13)	0.01	1.54 (1.07 – 2.16)	0.02
Pacific	764 (14.6)	45 (5.9)	719 (94.1)	1.36 (0.98 – 1.88)	0.07	1.40 (0.96 – 1.99)	0.07
Asian	608 (11.6)	13 (2.1)	595 (97.9)	0.49 (0.28 – 0.86)	0.01	0.50 (0.27 – 0.84)	0.02
Presence of eczema	1198 (22.9)	65 (5.4)	1133 (94.6)	1.25 (0.95 – 1.65)	0.11	1.24 (0.93 – 1.63)	0.13
NZiDep ≥3	1270 (24.3)	65 (5.1)	1205 (94.9)	1.16 (0.88 – 1.53)	0.30	0.99 (0.73 – 1.33)	0.96
Household crowding	951 (18.2)	45 (4.7)	906 (95.3)	1.04 (0.76 – 1.43)	0.81	0.91 (0.64 – 1.29)	0.61

Table 46 footnote: Sampled anatomical sites were the anterior nares, oropharynx, and antecubital fossa. 'Co-colonisation' refers to colonisation with both *S. pyogenes* and *S. aureus*, but not necessarily at the same anatomical site. The NZiDep is an individualised measure of deprivation derived from questionnaire responses

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Table 47: Unadjusted and multivariable log-binomial adjusted associations between skin and soft tissue infection (SSTI) and *Streptococcus pyogenes* sole colonisation, *Staphylococcus aureus* sole colonisation, and co-colonisation with both organisms.

Explanatory variable	**Total, n (%)**	**SSTI diagnosis, n (%)**		**Unadjusted analyses**		**Multivariable analyses**	
		Yes	**No**	**RR (95% CI)**	**P-value**	**aRR (95% CI)**	**P-value**
Total	5235 (100.0)	643 (12.3)	4592 (87.7)				
S. pyogenes sole colonisation	284 (5.4)	35 (12.3)	249 (87.7)	1.05 (0.76 – 1.45)	0.76	1.02 (0.72 – 1.38)	0.90
S. aureus sole colonisation	2027 (38.7)	250 (12.3)	1777 (87.7)	1.09 (0.93 – 1.27)	0.29	1.05 (0.90 – 1.23)	0.54
S. pyogenes + *S. aureus* co-colonisation	240 (4.6)	56 (23.3)	184 (76.7)	1.99 (1.56 – 2.53)	<0.0001	1.74 (1.17 – 2.64)	0.008

Table 47 footnote: Sampled anatomical sites were the anterior nares, oropharynx, and antecubital fossa. 'Sole colonisation' refers to colonisation with one of the two organisms but not the other. 'Co-colonisation' refers to colonisation with both organisms. Co-colonisation need not have been at the same site. Multivariable analyses have been adjusted for sex, ethnicity, eczema, socioeconomic deprivation, and household crowding.

CHAPTER 11: CONCLUSIONS

11.1 SUMMARY OF FINDINGS

This thesis has demonstrated significant disparities across a range of infectious disease (ID) related health outcomes for Māori and Pacific children in the *Growing Up in New Zealand* (GUINZ) longitudinal birth cohort. In general, these disparities remained apparent when socioeconomic status and related household environmental exposures were accounted for using multivariable regression models. Outcomes described included hospitalisation for an ID, community antibiotic use (an approximation of community ID rates, albeit with some caveats as described below), and skin and soft tissue infection (SSTI) rates. Disparities on the basis of socioeconomic status were also consistently identified across the range of outcomes examined in this thesis, though the increased risk associated with socioeconomic deprivation was generally lower than that observed for ethnicity. The association between poverty and infectious disease is well documented in NZ and internationally.

These ethnic disparities identified within the GUINZ cohort are consistent with previous findings from the NZ population at large, such as from Baker *et al*. (1), and are similar to disparities identified between the European majority populations and indigenous or ethnic minority groups in comparable countries such as Australia, Canada, and the United States of America (USA) (2, 9). Chapter 2 of this thesis consisted of a literature review examining these ethnic disparities both in NZ and in these comparable countries, and identified consistent patterns of ID related health disadvantage for indigenous and ethnic minority groups. These disparities were present across a range of ID outcomes including rates of hospitalisation for an ID, rates of SSTI, and rates of infection with specific pathogens such as *Staphylococcus aureus*. This chapter also examined potential causes for the ethnic disparities identified, with evidence presented showing an important role for socioeconomic deprivation, household crowding and poor housing quality, reduced healthcare access and lower health literacy, and both interpersonal and institutional racism within the healthcare system.

Chapter 4 of this thesis explored several methods of ascribing ethnicity, including self-prioritisation, total response, and single combined ethnicity methods. Although none of the methods of ascribing ethnicity were perfect, this study determined that the self-prioritised

ethnicity method was the most suitable for use in the subsequent studies in this thesis. This was because it had the advantage of simplicity of presentation for an international audience and was able to maintain subgroup size and statistical power within ethnic subgroups and for the less common outcomes used in later projects. However, for future studies intended for a NZ audience, with larger sample sizes and common outcomes, or for sociological research in which ethnic diversity is of primary interest in itself, single-combined ethnicity would be the preferred method. This is because the single-combined method better respects participant autonomy in identifying with multiple ethnicities, and was able to identify a diversity of levels of risk within the ethnic groups defined by the other methods. However, single-combined ethnicity is seldom used in biomedical research making comparisons with prior research less straightforward. Large sample sizes are required for the single-combined method as it generates a number of ethnic combination groups that have relatively few participants in them, leading to problems maintaining statistical power for these groups.

Chapter 4 also compared household income with individualised (NZiDep), and area-level (NZDep2013) indices of socioeconomic deprivation. Household income was not able to be used due to non-random missing data and a mixture of pre- and post-tax amounts being collected, both leading to a risk of bias. This is an established problem with income data obtained from surveys (159). While international evidence suggests that income estimation error can go either way (under estimates being particularly common when tax liability is in question) (160), in Chapter 4 people living in more deprived areas were more likely to provide post-tax amounts or to not respond to the question. Previous research indicates that these estimation errors can be informational, computational, or motivational; efforts to improve response rates and accuracy should focus on these factors (160). The individualised NZiDep and the area-level NZDep2013 indices of deprivation both performed well and were used in subsequent studies in this thesis, depending on which covariates were to be included in multivariable models. The NZiDep has the advantage of avoiding the ecological fallacy – i.e. making assumptions about an individual group member based on characteristics of the group or environment (165).

Chapter 5 used community pharmacy dispensing data to show that the number of courses of antibiotics prescribed per child in NZ was very high in comparison with other countries; this finding should be of concern to both prescribers and the general public in NZ. Community

antibiotic dispensing is of interest in itself as an antimicrobial stewardship issue, but also serves as an approximation of the burden of ID managed in the community. However, there are some caveats with this interpretation of community antibiotic dispensing data. Firstly, a child must have access to healthcare to receive a prescription, so the most deprived children may be undercounted. And secondly, there are doctor and patient factors which influence the decision to prescribe, so for example a child who is deemed unlikely to reattend if worsening may be more likely to receive an antibiotic, and a doctor who has limited time in a busy practice may be more inclined to prescribe rather than educate.

As described in chapter 5, Māori and Pacific children were found to receive a greater number of courses of antibiotics in the first five years of life, and to receive their first course of antibiotics at a significantly younger age, compared with European and Asian children. This likely reflects a higher incidence of ID managed in primary care amongst Māori and Pacific children but may also reflect on the quality of care received. Primary care doctors in NZ are well aware that Māori and Pacific children are at higher risk of complications of recurrent infection such as rheumatic fever and bronchiectasis, and are therefore likely to maintain a lower threshold for antibiotic treatment than they use for lower risk children. However, the preponderance of amoxicillin use and marked seasonality suggested that much of the observed antibiotic use was for winter upper and lower respiratory tract infections, which are largely viral and do not require antibiotic treatment. Unrestrained antibiotic use encourages the development and spread of resistant organisms in the population at large. It also places the individual at risk of antibiotic-related harm, such as allergic reactions and gastrointestinal side effects, while being of little benefit when used to treat self-limiting illnesses. Furthermore, recent research suggests possible links between early life antibiotic use and the development of atopic disease and weight gain, both likely mediated through antibiotic-induced changes in the host microbiome (176, 178, 186, 283).

Chapter 6 showed that hospitalisation for an ID affected over a quarter of NZ children before the age of five years. This chapter identified several risk factors for hospitalisation with an ID, such as duration of breastfeeding and lack of household heating, which could be amenable to targeted governmental policy interventions. Addressing other risk factors including socioeconomic deprivation and household crowding would require political commitment and broader economic efforts over a longer time frame. Reduced access to primary care was

associated with an increased risk of hospitalisation. It should be noted that access to care is determined by a number of direct and indirect costs; the direct cost to families is now very low as primary care is free of charge for children in NZ. The indirect costs of accessing care are not necessarily amenable to being addressed from within the healthcare system and relate more to the socioeconomic resilience of households. Māori and Pacific children were more likely to experience reduced access to primary care, and were more likely to be admitted to hospital for an ID. The increased risk of hospitalisation for Māori and Pacific children remained after accounting for the effect of reduced access to care and a broad range of covariates including socioeconomic deprivation and features of the household environment. Chapter 6 concluded that the high rates of hospitalisation for ID seen amongst Māori and Pacific children are likely to be on the basis of residual confounding due to the confluence of multiple adverse social determinants of health in these ethnic groups, with a likely contribution from additional unmeasured factors.

Chapter 7 investigated the impact of *S. aureus* colonisation status and selected host and environmental variables on risk of SSTI. Māori and Pacific children were found to suffer from higher rates of skin and soft tissue infection (SSTI), and were more likely to be hospitalised for an SSTI; hospitalisation for an SSTI affected 4.2% of Māori children and 8.2% of Pacific children compared with 2.0% of European/Other children. The rates of hospitalisation for SSTI for Māori and Pacific children were amongst the highest identified in comparable developed countries (9, 15). Colonisation with *Staphylococcus aureus* was found to be associated with SSTI and the relationship was stronger for SSTI outcomes in the year prior to swab collection and where the site of colonisation was the skin. Children of European/Other ethnicity were found to be more likely to have heavy nasal colonisation, a proxy for the persistent nasal carrier state (43). Most previous studies into the *S. aureus* carrier state have focussed on nasal carriage in adult populations. This chapter supports recent evidence that colonisation status at other anatomical sites, particularly the oropharynx, is equally important in children (233).

Chapter 8 further investigated the role of *S. aureus* in the risk of community-onset SSTI by looking at the impact of colonisation with methicillin-resistant *S. aureus* (MRSA). Within the subset of children colonised with *S. aureus*, Māori and Pacific children were more likely to be colonised with a MRSA isolate, as were children living in more crowded or more

socioeconomically deprived households. The reasons why these population groups are more prone to colonisation with MRSA are unclear; the social determinants of disease would be expected to equally favour the transmission of methicillin-susceptible *S. aureus* within households. In Chapter 5, Māori and Pacific children were found to have received a greater number of courses of antibiotics in the first five years of life. This increased antibiotic exposure could plausibly lead to an increased risk of acquiring an antibiotic resistant organism.

Colonisation with an MRSA isolate was associated with a higher risk of community-onset SSTI in the year prior to the interview conducted at 4½ years of age. This association between MRSA colonisation and risk of SSTI supports previous research which has linked the spread of community-acquired MRSA strains with an increase in the incidence of SSTI. However, this association may not be causal. As the timing of MRSA acquisition was not known, it is possible that an SSTI could have been caused by an organism other than MRSA, and then been treated with antibiotics which could have led to an increased risk of MRSA acquisition.

Chapter 9 examined the effect of colonisation with particular genotypes (*spa* clonal complexes) of *S. aureus* on the risk of SSTI in the year prior to swab collection. This was only possible in the subset of *S. aureus*-colonised children for whom an isolate was available for typing. In unadjusted analyses, several *S. aureus* genotypes appeared to be associated with an increased risk of SSTI, but this was not confirmed by multivariable analyses, which showed that eczema and ethnicity were the main factors which determined risk of SSTI. Confounding due to minor differences in the distribution of *S. aureus* strains across ethnic groups might have explained the apparent differences in unadjusted analyses.

These findings suggest that efforts to reduce the risk of SSTI should focus on addressing the underlying disparities in the social determinants of health rather than on attempting to identify and eradicate specific high-risk strains of *S. aureus*. The finding that *S. aureus* genotype was not associated with risk of SSTI appears somewhat contradictory when viewed together with the finding from Chapter 8 that MRSA status – another genetic feature of the colonising organism – was important. It was possible for both MRSA and non-MRSA strains of *S. aureus* to share the same *spa*-type, suggesting that *spa*-typing might not have been able to

account for the distribution of virulence factors such as methicillin resistance in a way that accurately categorised risk.

Chapter 10 investigated the role of *Streptococcus pyogenes* in SSTI and identified several novel findings. *S. pyogenes* colonisation was associated with an increased risk of SSTI in the year prior to swab collection. In addition, the ethnic pattern of risk of *S. pyogenes* colonisation matched the ethnic pattern of risk of SSTI. While colonisation was predominantly in the oropharynx and thus distant from the focus of infection on the skin, there was some previous published evidence in support of this association (280, 281). However, previous studies conducted in tropical northern Australia and in developing countries where recurrent SSTI is endemic have suggested that oropharyngeal colonisation with *S. pyogenes* is less common in these settings (20). It is possible that the relationship we observed was due to underlying factors which led to both an increased risk of SSTI and an increased risk of *S. pyogenes* oropharyngeal colonisation. Household crowding or the number of children in the home would seem like plausible factors which could predispose to both SSTI and *S. pyogenes* colonisation, but this chapter did not identify a significant relationship between crowding and colonisation.

Co-colonisation with both *S. pyogenes* and *S. aureus* was even more strongly associated with SSTI. When co-colonisation was considered, colonisation with either organism alone was no longer associated with an increased risk of SSTI. *S. pyogenes* and *S. aureus* are frequently isolated together from infected skin lesions, particularly in impetigo, which provides some indirect support for this finding (29). The potential for confounding exists as co-colonisation also shared a similar ethnic pattern of risk with SSTI. As co-colonisation was uncommon, identifying and treating co-colonised children to reduce the burden of pathogenic colonising bacteria would be a feasible intervention to subject to further study.

In summary, the key findings of this thesis are that:

- Ethnic disparities in ID outcomes seen in Māori and Pacific people in NZ are consistent with similar patterns of health disadvantage seen in indigenous and ethnic minority populations in comparable countries such as Australia, Canada, and the USA.

- NZ children receive more antibiotics than children in comparable developed countries, and Māori and Pacific children receive more than European or Asian children, likely due to a higher rate of community ID and differences in prescribing practices.
- Hospitalisations for ID in general, and for SSTI in particular, were common in NZ and disproportionately affected Māori and Pacific children. Some potentially modifiable risk factors were identified.
- The burden of SSTI managed in the community was many times greater than that managed in the hospital, and was also experienced disproportionately by Māori and Pacific children.
- Colonisation with *S. aureus* and colonisation with *S. pyogenes* were associated with an increased risk of SSTI. While the genotype of the colonising strain of *S. aureus* did not appear to influence the risk of SSTI, methicillin resistance of the colonising strain was associated with an increased risk. Co-colonisation with both *S. aureus* and *S. pyogenes* was associated with a high risk of SSTI, and when co-colonisation was taken into account, colonisation with either organism alone was no longer associated with an increased risk of SSTI.

11.2 DIRECTIONS FOR FUTURE RESEARCH

The findings of this thesis suggest the following as key priorities for future research:

Improving antimicrobial prescribing in primary care

- Link primary care diagnostic and prescribing data to assess the appropriateness of antibiotic prescribing for NZ children. However, as relevant diagnostic information is frequently documented within the free text of the clinical record, it could require a significant amount manual work to extract this data. The GUINZ cohort is well set up to contribute to this research as a team working within GUINZ has already obtained general practice clinical records for children still resident within the Auckland, Counties-Manukau and Waikato District Health Boards. After manual identification of key words, the team used a computer programme to ‘read’ the free text component of

these records to identify key words associated with a diagnosis of otitis media. These diagnoses were then confirmed by a researcher. This process could be replicated to identify other forms of infection such as lower respiratory tract infection and SSTI. If such data could be obtained in a timely and automated fashion, then it could be used to provide prescriber feedback and the effect of this feedback on prescribing rates could also be assessed.

Addressing the high rate of hospitalisation for infectious diseases and disparities in this rate

- Identify and assess the impact of additional factors that might plausibly be associated with a risk of hospitalisation for an ID, but which were not obtained in the GUINZ interviews. Such factors might include healthcare-seeking behaviour and health literacy amongst others.
- Determine how recent changes in the availability of fees-free primary healthcare have affected access to healthcare and health outcomes such as rates of hospitalisation for ID and for non-infectious chronic conditions such as asthma and eczema.

Investigating host factors which affect risk of S. aureus or S. pyogenes colonisation or of SSTI

- This thesis used a relatively limited list of host factors that were able to be obtained from data collected in the GUINZ interviews – sex, ethnicity and the presence of eczema. Further research is needed to examine host factors, both behavioural and genetic, which predispose either to *S. aureus* or *S. pyogenes* colonisation or to infection. Research of this sort might suggest interventions that could be trialled to attempt to reduce the rate of SSTI. A number of candidate genes which relate to immune molecules and substances secreted into nasal mucus have been identified which appear to predispose to *S. aureus* nasal colonisation (23). More recent genome-wide association studies have also identified a small number of possible gene loci associated with colonisation (284, 285). However, attempts to identify host genetic variants that contribute to susceptibility to *S. aureus* infection through genome-wide association studies or whole genome sequencing have not yet led to conclusive results (237).

- The findings of this thesis are consistent with the view that ethnicity functions as a marker for the clustering of socioeconomic risk factors leading to confounding, although unmeasured behavioural or environmental factors may also play a role. However, ethnicity is tied to ancestry (albeit somewhat loosely), so there is some genetic variation between ethnic groups. The amount of variation is small compared with inter-individual variation within groups (28, 152). Given the higher rates of SSTI seen in Māori and Pacific children, if studies were to be undertaken looking at the genetic determinants of risk of SSTI, care would have to be taken that genetic markers of ancestry are not confused with markers of risk. While looking for a genetic explanation for conditions with a significant social gradient is rightly controversial, if a genetic link is found this can counter-intuitively serve to de-stigmatise the condition. Similar research in adults with gout has identified predisposing gene variants carried by some Pacific people (286, 287). As the individual has no control over their complement of genes, this finding helps to reduce the stigma associated with a diagnosis of gout, which people often assume is due to poor food choices or alcohol consumption. A case-control study using a genome-wide association study approach to look at a well-defined phenotype (e.g. recurrent cutaneous abscess) would be a relatively cost-effective way to include more host information and such a study could potentially be nested within GUINZ.

Investigating the relationship between bacterial colonisation and risk of SSTI

- Investigate the dynamics of *S. aureus* and *S. pyogenes* colonisation at multiple anatomical sites over weeks to months in pre-school and school-aged children. In particular the *S. pyogenes* oropharyngeal carrier state is not well characterised and deserves further study. If combined with documentation of incident SSTI, research of this type could determine whether colonisation with a new strain of either organism was followed by a period of increased risk of SSTI. This type of study could also determine the temporal relationship between MRSA acquisition, or the acquisition of *S. aureus* and *S. pyogenes* co-colonisation, and risk of SSTI. A study of this type could be performed using a voluntary subset of children in the GUINZ study, or in a school-based study setting.

- While this thesis did not support a link between bacterial genotype and risk of SSTI, the finding that MRSA was associated with a greater risk of SSTI suggests that some

differences between bacterial strains are important. An alternative method of bacterial genotyping which combines markers of lineage with the ability to identify genes for virulence factors might be better able to identify whether particular strains of *S. aureus* and *S. pyogenes* are associated with an increased risk of SSTI.

- Related interventional studies could aim to reduce the incidence of SSTIs in high-risk children, such as those with *S. aureus* and *S. pyogenes* co-colonisation, recurrent SSTI, or a predisposing skin condition such as eczema, by attempting to eradicate or reduce the burden of colonising pathogenic bacteria. Possible approaches to decolonisation that are currently in clinical use include topical nasal and skin disinfectants, with or without systemic antibiotics (264). Novel approaches could include manipulation of the microbiome, such as by introduction of high concentrations of strains of benign bacteria (such as *Staphylococcus epidermidis* or *Staphylococcus hominis*) which are able to suppress *S. aureus* (228).

- MRSA carriage was found to be more common in Māori and Pacific children, who were also found to receive a higher number of courses of antibiotics in the first five years of life. These findings are possibly related, and future research could investigate whether receipt of antibiotics has an effect on MRSA carriage rates that is independent of the effect of ethnicity. Investigating a temporal relationship between the receipt of antibiotics and colonisation with MRSA fell outside the scope of this thesis, but the data required for such an investigation are readily available within GUINZ using the data sources used in this thesis.

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and Caucasian, but not Maori, case and control sample sets. Human molecular genetics. 2010;19(24):4813-9.

LIST OF PUBLISHED PAPERS

The following published papers have been included as chapters in this thesis.

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