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YLIOPISTO**
UNIVERSITY
OF TURKU



**MANDATES
AND INCENTIVES:
IMPLEMENTING FINLAND'S
FIRST VACCINATION
CAMPAIGN AGAINST
SMALLPOX**

Susanna Ukonaho



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“Future nations will know by history only that the loathsome smallpox has existed and by you has been extirpated.”

Thomas Jefferson, 1806
In a letter to Edward Jenner

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ABSTRACT

Despite the development of modern medicine and vaccines, vaccine-preventable childhood infections remain a major burden and even cause of death around the globe. The recent surge in the outbreaks of infectious diseases such as measles and pertussis, together with the severity of the COVID-19 pandemic, have spurred a worldwide search for functional strategies to increase vaccine uptake. This thesis focuses on 18th and 19th century Finland, where before vaccines smallpox was a leading cause of death, killing up to 11% of Finland's population around 1800. While vaccination against smallpox started in 1802 and eventually eliminated smallpox from Finland in 1941, little is known about how this vaccination campaign was implemented, and to what extent it was successful. In this thesis, I investigated the implementation of Finland's first vaccination campaign through three key factors: vaccination mandates (**Chapter I**), socio-economic status (**Chapter II**), and the family network (**Chapter III**). To do this, I collected and analysed a series of unique historical records provided by the Finnish National Archives.

First, this thesis showed that mandatory vaccination was successful in improving vaccination coverage by 20% during Finland's first vaccination campaign, where mean coverage surpassed 80% coverage required for herd immunity against smallpox. However, the law had varied impact on the socio-economic groups. While the >80% coverage of the high socio-economic group was unaffected by the law, the middle socio-economic group saw substantial improvement in coverage after the law. The lowest socio-economic group with initially poor coverage, showed little increase, highlighting the necessity for additional interventions. Though grandmothers improved in child survival from many infectious diseases, including smallpox, they had no effect on vaccine uptake, underscoring the need for alternative strategies to promote vaccination.

These findings enable public health workers to make informed decisions on the strategies to combat declining vaccination coverage. Understanding the success of past vaccination initiatives can help in the management of future outbreaks and offer general conclusions applicable to contemporary vaccination campaigns.

KEYWORDS: smallpox, vaccination, historical societies, evolutionary medicine

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TIIVISTELMÄ

Modernin lääketieteen ja rokotteiden kehityksestä huolimatta rokotteilla ennaltaehkäistävät lapsuusajan infektioaudit ovat yhä merkittävä kuolinsyy ympäri maailmaa. Viimeaikainen kasvu tartuntatautitapausten, kuten tuhkarokon ja hinkuyskän, määrässä on korkean tulotason maissa yhdessä COVID-19 pandemian kanssa johtanut globaaliin pyrkimykseen löytää toimivia strategioita, jotka lisäävät rokotuskattavuutta ja torjuvat rokotevastaisuutta. Tämän väitöskirjan tutkimusväestössä 1700- ja 1800-luvun Suomessa isorokko oli merkittävä kuolinsyy lapsilla, tappaen jopa 11% Suomen väestöstä noin vuonna 1800 ennen rokotteiden käyttöönottoa. Rokotukset isorokkoa vastaan aloitettiin vuonna 1802 ja vaikka isorokko saatiin lopulta onnistuneesti hävitettyä Suomesta vuonna 1941, isorokkorokotuskampanjan toteutusta ja onnistumista on tutkittu hyvin vähän. Tämä väitöskirja tutkii Suomen ensimmäisen rokotuskampanjan toteutusta ja seurauksia kolmen avaintekijän kautta: rokotuslait (**Chapter I**), sosioekonominen asema (**Chapter II**) ja perheverkosto (**Chapter III**). Tutkielmaa varten Kansallisarkistosta kerättiin ja analysoitiin ainutlaatuisia historiallisia aineistoja.

Väitöskirjani osoitti, että rokotuslaki onnistui nostamaan rokotuskattavuutta 20%:lla Suomen ensimmäisen rokotuskampanjan aikana, minkä ansiosta keskimääräinen kattavuus ylitti 80%:n isorokon laumasuojan rajan. Rokotuslailla ei kuitenkaan ollut yhtenäistä vaikutusta rokotuskattavuuteen kaikissa sosioekonomisissa ryhmissä. Hyväosaisten sosioekonomisen ryhmän yli 80%:n rokotuskattavuus pysyi ennallaan rokotuslain voimaantulon jälkeen, kun taas keskitason sosioekonomisen ryhmän rokotuskattavuus parani huomattavasti lain jälkeen. Laki ei sen sijaan riittävästi tavoittanut huono-osaisinta sosioekonomista ryhmää, jolla oli alhaisin rokotuskattavuus, osoittaen lisätoimenpiteiden tarvetta. Vaikka isoäidit paransivat selviytymistä joiltain tartuntataudeilta, mukaan lukien isorokolta, perhesiteet eivät vaikuttaneet rokotuskattavuuteen. Viranomaisten onkin löydettävä muita lähestymistapoja kannustaakseen perheitä lapsiensa rokotamiseen.

Tulokseni auttavat julkisen terveydenhuollon ammattilaisia tekemään perusteltuja päätöksiä rokotusohjelmien suunnittelussa. Aiempien rokotusaloitteiden menestyksen ymmärtäminen voi auttaa tulevien epidemioiden hallinnassa, tarjoten yleisiä päätelmiä, jotka ovat sovellettavissa nykyaikaisiin rokotusohjelmiin.

ASIASANAT: isorokko, rokotukset, historialliset yhteisöt, rokotuslaki, rokotuskattavuus

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Abbreviations

WHO	World Health Organization
ICU	Intensive care unit
SEG	Socio-economic group
GLM	General linear model
GLMM	Generalized linear mixed model
GAMM	Generalized additive mixed model
AICc	Corrected Akaike Information Criterion
GDP	Gross Domestic Product
MMR	Measles, mumps and rubella (vaccine)

List of Original Publications/Manuscripts

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

- I **Ukonaho S**, Lummaa V*, Briga M*. The long-term success of mandatory vaccination laws after implementing the first vaccination campaign in 19th century rural Finland, *American Journal of Epidemiology*, 2022; **191**(7): 1180–1189.
- II **Ukonaho S**, Lummaa V, Briga M. Effectiveness of mandates in improving infant vaccination coverage across socio-economic groups: a study of Finland's first vaccination law.
- III **Ukonaho S**, Chapman SN, Briga M*, Lummaa V*. Grandmother presence improved grandchild survival against childhood infections but not vaccination coverage in historical Finns. *Proceedings of the Royal Society B*, 2023; **290**(1999): 20230690.

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1 Introduction

1.1 Contemporary vaccination campaigns

Infectious diseases pose a significant public health challenge across all age groups, with children being particularly susceptible (Morens et al., 2004; Naghavi et al., 2017). To this day, childhood infections such as pertussis and measles persist as leading causes of death among children under 5 years old in low- and middle-income countries (GBD 2019 Diseases and Injuries Collaborators, 2020; Kassebaum et al., 2017), and high-income countries are experiencing a resurgence of these infections despite the vaccines being readily available (Dabbagh et al., 2017; Gardner et al., 2020; Hotez et al., 2020; Lo et al., 2017; Olive et al., 2018; Omer et al., 2009; Phadke et al., 2016). While the causes for these outbreaks are complex and vary geographically, two important contributing factors are: (i) vaccine hesitancy, marked by partial or delayed acceptance or outright refusal of vaccination (World Health Organisation, 2014), and (ii) limited access to vaccines (Betsch et al., 2018; Thomson et al., 2016; World Health Organisation, 2014). Ultimately the decline in vaccine uptake poses a substantial obstacle to preventing and controlling the spread and achieving local elimination of infectious diseases, creating a severe risk for communities where not everyone can be vaccinated, including those with certain medical conditions or allergies. Attaining the necessary vaccination coverage for infectious diseases becomes increasingly challenging due to spatial clustering of the unvaccinated groups, creating potential sources for the re-emergence and spread of infections to other regions (Masters et al., 2020).

Vaccination is a cost-effective public health strategy for eliminating infectious diseases globally. For example, the COVID-19 vaccine has saved an estimated 14 million lives within a year and has mitigated the severity of infection among vaccinated people (Tenforde et al., 2022; Watson et al., 2022). Although vaccines have been a key public health tool for over 200 years, the strategies behind a successful vaccination campaign have not been identified and the long-term impact of vaccine mandates in increasing vaccination coverage remain unknown. Achieving high coverage is difficult and expensive but essential for meeting public health targets on both national and international scales, including for example during the COVID-19 pandemic in managing intensive care unit (ICU) overload (Moreno-

Mulet et al., 2021) or meeting the regional World Health Organization (WHO) elimination goals for measles and rubella (World Health Organisation, 2020). The resurgence of measles and other childhood infections and the severity of the COVID-19 pandemic have spurred a global search for effective strategies to improve vaccine uptake, especially among the vaccine-hesitant population.

1.2 The history of the smallpox vaccination campaign

The first infectious disease successfully eradicated worldwide is smallpox, which was eradicated after near 200 years of vaccination efforts globally. Smallpox was among the most lethal diseases in human history (Duncan et al., 1993; Krylova et al., 2020; van Panhuis et al., 2013). For example, in my study population in 18th and 19th century Finland, up to 11% of Finland's population died from smallpox around 1800 before the development of the first vaccine by the British physician Edward Jenner in 1796 (Ketola et al., 2021; Pitkänen et al., 1989).

Finland began its first vaccination campaign in 1802 along with other European countries (Björkstén, 1908). Many of these countries soon followed with vaccine mandates, for example as early as 1806 in parts of Italy, 1816 in Sweden, 1853 in England and Wales and 1874 in Germany (Salmon et al., 2006). However, historical records describe that in Finland the distribution of vaccines improved gradually (Figure 1) (Björkstén, 1908). In 1825, Finland was divided into vaccination districts supervised by a district doctor, who received annual reports from the vaccinators, who were mostly priests and public officers. Priests not only promoted vaccination, but also prepared lists of unvaccinated individuals who were called for free vaccination during church service. Since there was often a lack of vaccinators, it was common for vaccinators to travel long distances and multiple parishes, where due to lack of proper public healthcare, vaccinations were carried out in a randomly selected location. As a novel method, the smallpox vaccine received hesitancy and opposition from the public, which remained strong despite the attempted reassurance by the clergy (Björkstén, 1908). Because vaccination coverage failed to reach the 80% required for herd immunity, and reduction in vaccinations during the famine years 1866–1868 led to several large smallpox outbreaks in the early 1870s, mandatory-vaccination law was adopted in 1883 (Björkstén, 1908; Pitkänen et al., 1989). The law required parents to vaccinate children by the age of two years, and was gradually enforced with a fine (Björkstén, 1908). The last case of smallpox in Finland was recorded in 1941, but routine vaccinations continued until 1980 (Pitkänen et al., 1989), when smallpox was declared eradicated worldwide by WHO (Fenner et al., 1988).

In 19th century Finland, smallpox vaccine was a major public health tool to combat communicable diseases and the only available vaccine at that time. However, the characteristics and implementation of the smallpox vaccination campaign have been rarely studied (van Panhuis et al., 2013), even though there is still an urgent need today to address barriers to vaccination. In this thesis, I investigate the implementation of Finland's first vaccination campaign against smallpox in a historical society before modern medical care.

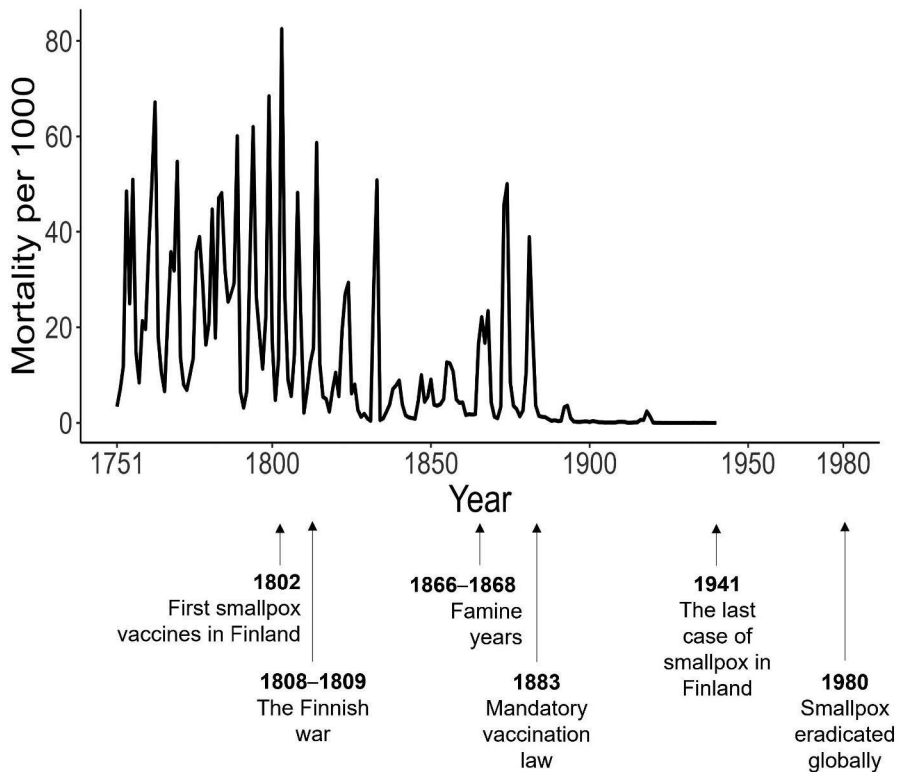


Figure 1. Smallpox mortality in Finland during the 18th and 19th century and major historical Finnish events. Original data from Pitkänen, Mielke and Jorde 1989 (Pitkänen et al., 1989).

1.3 Factors influencing vaccination coverage

1.3.1 Vaccine mandates

Vaccination laws, the mandatory vaccination of individuals, is one approach recently taken by several countries (2017 in Italy, 2018 in France and 2020 in Germany) to combat declining vaccination coverage (Gori et al., 2020; Lévy-Bruhl et al., 2019;

Neufeind et al., 2021). These laws use fines to regulate children's access to public schools or collective child services based on vaccination status (Garnier et al., 2020; Gori et al., 2020; Lévy-Bruhl et al., 2019; Neufeind et al., 2021; Nyathi et al., 2019; Seward et al., 2002). However, exemptions to these laws have been granted for medical and nonmedical reasons, which has led to pockets of low vaccination coverage in the United States (Garnier et al., 2020; Wang et al., 2014). Hence, the effectiveness of vaccination laws at increasing vaccination coverage is unclear. Preliminary studies suggest that these vaccination mandates have succeeded in improving vaccination coverage in Italy, France and California on the short-term (Gori et al., 2020; Lévy-Bruhl et al., 2019; Nyathi et al., 2019), but the long-term effects of these laws remain unknown.

1.3.2 Socio-economic differences

Vaccination laws are often assumed to apply universally, without exemptions, but their impact on vaccination coverage across different socio-economic groups remains unclear. Finding solutions that improve vaccination coverage for all is important particularly for the communities struggling with low vaccination coverage, as they are at risk for a larger incidence of vaccine preventable diseases (Domai et al., 2022; McLaughlin et al., 2022; Rane et al., 2021). Mandatory vaccination could be used as a tool to protect these communities if it provided equal protection against infectious diseases. However, individuals with low socio-economic status often have to overcome barriers to immunisation (McKinnon et al., 2021; Mills et al., 2022; Prickett et al., 2021; Sacre et al., 2022), which could undermine the impact of vaccination laws. Because communities with low vaccination coverage are often clustered, they can put the rest of the population at risk of outbreaks (Masters et al., 2020) and hinder elimination goals (World Health Organisation, 2020).

1.3.3 Family networks

As vaccination against smallpox in Finland was voluntary for 80 years before the mandatory vaccination law, positive attitudes towards vaccines within the family were likely important in encouraging the uptake and timing (i.e., earlier) of vaccination against childhood infections. Indeed, in many contemporary families, grandmother's opinion affects parents' attitudes towards vaccines (Karthigesu et al., 2018). For example, grandmother's opinion was rated in the top two contributing factors on parents' decisions on child health issues in a study from 20th century Lebanon (Atiyeh et al., 2005), and in the UK, positive attitudes among Indian grandparents towards the measles, mumps and rubella (MMR) vaccine correlated

with high grandchild vaccination coverage compared to their peers (Mixer et al., 2007).

Identifying the role of grandmothers in vaccine uptake could provide insights into the mechanism behind their influence on improving the survival of their grandchildren. The contribution of grandmothers to the improvement of grandchild survival is well established in several historical and contemporary societies (Beise, 2005; Beise et al., 2002; Chapman et al., 2021; Leonetti et al., 2004; Sear et al., 2000; Sear et al., 2008), but the underlying mechanisms remain unclear. One way grandmothers could have improved the survival of grandchildren is through providing knowledge in childcare (Aubel et al., 2004; Karmacharya et al., 2017; Simkhada et al., 2010), which could have been particularly critical during sickness and epidemics. To the best of my knowledge, the effect of grandmother presence on grandchild survival from childhood infections in historical societies has not been studied before.

1.4 Aims of the Thesis

The aim of this thesis is to understand the characteristics and the implementation of the smallpox vaccination campaign in historical Finland and the long-term impact of mandatory vaccination on vaccination coverage. For the purpose of this thesis, I digitized a series of unique historical vaccination, birth and death and socio-economic status records maintained by district doctors and the clergy from southwest and central-eastern Finland (Table 1).

- 1) **Chapter I** had 2 aims. First, I describe the seasonal dynamics of the vaccination campaign and the age groups that were targeted. The timing of vaccination is important, as late vaccination leaves the individual susceptible to infections, while early vaccination can be ineffective due to maternal antibodies (Zimmermann et al., 2019) and in the case of smallpox can also have considerable negative side effects (Cono et al., 2003; Kempe, 1960). Second, I tested two hypotheses, namely:
 - (i) Did the vaccination law cause a long-term increase in vaccination coverage (**Chapters I & II**)
 - (ii) Did the vaccination law decrease the spatio-temporal variance in vaccination coverage.

Increasing vaccination coverage and reducing its spatiotemporal variance are important because there is a risk this variance can create pockets of susceptible individuals from which epidemics can emerge (Keeling et al., 2011). This phenomenon can become an issue because vaccination behaviours can cluster within populations and pose a risk of disease outbreak

(Masters et al., 2020). Before the vaccination law, I expected to observe low vaccination coverage and high variance at the age and timing of vaccination due to poor access to vaccines and high vaccine hesitancy, which I expected to stabilize after the vaccination law.

- 2) In **Chapter II**, I expanded the previous dataset of **Chapter I** and compared the impact of Finland's first vaccination law between different socio-economic groups. I investigated whether the vaccination law was able to equalize vaccination coverage between the socio-economic groups and protected the low socio-economic communities that could have barriers with accessing vaccines and vaccine hesitancy (McKinnon et al., 2021; Mills et al., 2022; Prickett et al., 2021; Sacre et al., 2022). I expected to find that vaccination laws promoted equality in vaccination and decreased differences between the socio-economic groups.
- 3) In **Chapter III**, I investigated the effect of family relationships (grandmother presence) on all-cause and cause-specific mortality of grandchildren, and grandchild vaccination coverage. I tested whether the beneficial effects of grandmothers on grandchild survival are mediated via improved survival from the childhood infections smallpox and measles, pulmonary infections, diarrhoea and/or via avoiding accidental deaths. The hypothesis was that if there are any beneficial effects of grandmothers on childhood survival from smallpox, these effects could be mediated via increased vaccination coverage.

Table 1. Summary of the aims and chapters of this thesis. No. Ind = Number of individuals.

CHAPTER	TOPIC	YEARS	PARISHES	DATASET	MODELS	NO. IND
I	Vaccine mandates	1837-1900	8	(i) Vaccination records (ii) Birth and death records	GLMM, Threshold model, GAMM	46,232
II	Socio-economic differences	1855-1900	10	(i) Vaccination records (ii) Birth and death records (iii) Occupational records	GLMM, Threshold model, GAMM	40,008
III	Family networks	1761-1900	12	(i) Multigenerational family records (ii) Vaccination records	CPH, GLMM	(i) 9,705 (ii) 1,594

2 Materials & Methods

2.1 Study population

In the 19th century, Finland was among the poorest agrarian societies in Europe (Kuisma, 2015) where agriculture, hunting, fishing and forestry made up over 60% of the GDP (Hjerpe et al., 1977; Rasila, 2003). At the time, the Finnish society was divided into four estates that all had governmental power over the estateless: nobility, clergy, bourgeoisie and landed farmers (*in finnish* = talonpojat). For over 600 years, Finland was an eastern province of the Kingdom of Sweden, until the annexation in 1809 when Finland became an autonomous grand-duchy in the Russian empire (The Finnish war, Figure 1). During this process, Finland retained its former laws, faith and official languages (Finnish and Swedish), and even the status of Finland as a state was debated, especially after Finland launched its own currency in 1863. Around the same time, the first railway was built in 1862 and the industrialization in Finland began at a slow pace. By the 20th century only around 10% of the population gained main livelihood from manufacturing.

In 1800, the average life expectancy was 39 years, which increased 7 years by 1900, and infant mortality was high around 20% (Turpeinen, 1979). Most people were estateless and poor, living in large multigenerational families, often close to the grandparents. Along with its neighbouring countries, Finland experienced a demographic transition beginning in the 1880s, leading to ageing population. Healthcare in the 19th century was very limited as there were only few doctors in the whole country and due to the lack of most modern innovations besides the smallpox vaccine from 1802 onwards (Björkstén, 1908). Smallpox vaccine remained the only vaccine provided by the Finnish government until the establishment of the Pasteur institute in 1916, distributing the rabies vaccine.

2.2 Data collection

2.2.1 Vaccination records

I photographed and digitized vaccination records manually from extensive district doctor archives held in the National Archives of Finland. These data include

information of the vaccinees, including the name, address, parents' occupation, age, timing and the level of success of the vaccination (as indicated by reported reaction to the vaccine: effective, mild, or no reaction) for each person (Figure 2A). Based on the accessibility and completeness of historical records, for **Chapter I**, I collected data from 8 rural parishes (Honkajoki, Ikaalinen, Jämijärvi, Karvia, Kustavi, Parkano, Rymättylä, and Tyrvää) from 1837–1899 (excluding records from 1847–1851, 1854, and 1856–1858 for 6 parishes and for Kustavi before 1862 and Rymättylä before 1865) that include information on 46,232 infant vaccinations (Tables 1 and 2, Figure 2B), with 26,328 from before and 19,935 records from after the introduction of the vaccination law. For **Chapter II**, I had data from 6 of the previously digitized parishes from southwest Finland (Ikaalinen, Karvia, Kustavi, Parkano, Jämijärvi and Honkajoki) and new data on 4 parishes from central-eastern Finland (Kuopio, Kuopio countryside, Tuusniemi and Maaninka). For these data, I had 40,008 individual vaccination records (Tables 1 and 2, Figure 2B), 21,395 records from before (1855–1882), and 22,638 from after the vaccination law (1883–1900). For **Chapter III**, I used vaccination data that matched the family history records from two parishes (Ikaalinen and Jämijärvi) between 1870 and 1900, which had in total 1594 individuals (Table 1, Figure 2B).

Table 2. Descriptive statistics on the vaccination data per parish.

Parish	Parish size	Mean number of vaccinated annually	Mean vaccination month	Mean vaccination coverage age <1 (%)	Vaccination coverage per socio-economic group		
					High	Middle	Low
Ikaalinen	7700	164	June	62	98	83	19
Jämijärvi	2200	48	June	59	64	90	11
Karvia	2500	56	July	65	82	77	10
Parkano	3000	128	July	81	61	83	27
Honkajoki	2100	38	June	52	71	70	7
Tyrvää	6600	146	June	73	NA	NA	NA
Kustavi	2200	43	June	95	119	83	52
Rymättylä	2200	44	July	64	NA	NA	NA
Kuopio city	6800	76	June	46	24	20	52
Kuopio countryside	12000	284	June	64	142	12	34
Maaninka	4200	139	June	92	138	102	54
Tuusniemi	6000	116	June	59	122	61	23

2.2.2 Demographic data

For **Chapter III**, I combined two datasets: (i) a large multigenerational demographic dataset of pre-industrial Finnish families (Chapman et al., 2021) and (ii) vaccination records (mentioned above) manually digitized from church records. The large multigenerational dataset of pre-industrial Finnish families were collected by local clergymen from 1749 onwards (Gille, 1949), and had digitized individual records on the birth, marriage and death dates and the cause of death from twelve parishes across Finland (Ikaalinen, Jämijärvi, Honkajoki, Tyrvää, Rymättylä, Karvia, Kustavi, Parkano, Hiittinen, Pulkkila, Rautu, Jaakkima) from 1761–1900. These years were selected because (i) there were little data before 1761, (ii) after 1900 smallpox outbreaks became rare, and to avoid (iii) the confounding effects modern public healthcare (Saarivirta et al., 2012) and (iv) the mortality decline during the 20th century (Scranton et al., 2016), which likely reduced the need for grandmother help (Chapman et al., 2024). I had data on in total 9705 individuals monitored from birth until the age of 15 years, of which 3857 individuals died before the age 15 (Table 1).

To study grandmothers' effect on the cause-specific mortality of the grandchildren, I identified and cleaned five causes of death from the demographic data: smallpox, measles, pulmonary infections, diarrhoeal deaths and accidents. These data included nearly half of all 3857 deaths of children under the age of 15. The causes of death were also selected based on how accurately they could be

identified by the local priests who had little to no experience in providing medical diagnosis. Smallpox and measles are both lethal childhood infections easily identified by their specific skin rashes although occasional misdiagnosis did occur (Pitkänen et al., 1989). In the 18th and early 19th centuries, as doctors were rare in Finland, the clinical diagnosis was often made by the inexperienced clergy, if at all, and in the absence of proper medical care sick children were cared for by the family (Saarivirta et al., 2012). Both smallpox and measles give a lifelong immunity for the survivors. For further details on smallpox and measles in historical Finland, see studies by Ketola et al. (Ketola et al., 2021) and Briga et al. (Briga et al., 2022). In this chapter, the umbrella term 'pulmonary infections' was used for all causes of death that were registered as pneumonia, tuberculosis and 'unknown respiratory infections', assuming that the priests had difficult consistently distinguishing between different pulmonary symptoms. Similarly, I grouped infections with diarrhoeal symptoms as 'diarrhoea' which included cholera, dysentery and typhoid fever. Accidental deaths also included many causes: drowning, suffocation, falls, burned in a fire, frozen in cold weather and kicked by a horse.

2.2.3 Socio-economic status

For **Chapter II**, individual's socio-economic status was obtained from the vaccination records, which had details on the vaccinated including occupation of the parent (mostly father's). In 19th century Finland, the social status of the whole family was tied to the husband's social status, and thus I used men's occupation as a reference of wealth and socio-economic status. The socio-economic status of an individual was categorised into three socio-economic groups (SEGs) based on the parents' occupation: high SEG, middle SEG or low SEG, following a previous study in the same population (Pettay et al., 2007). All the four estates (nobility, clergy, bourgeoisie and landed farmers) were classified as high SEG. However, the majority of the population was estateless, varying in relative wealth, but without any political representation, and these individuals were classified either in the middle, which included professions such as sharecroppers and craftsmen, or low SEGs, which included servants, dependent lodgers, and vagabonds. In total, I identified and translated 89 occupations from the vaccination records.

2.2.4 Estimation of vaccination coverage

I estimated vaccination coverage per parish and year using birth and death records from population census tables that have been validated by independent studies (Pitkänen, 1993; Voutilainen et al., 2020) and are kept at the National Archives of Finland. Additionally, I confirmed the accuracy of my own estimations of the annual

cohort sizes by comparing them to the 5–10 year census tables that had cohort sizes per parish. The vaccination coverage was calculated by dividing the annual number of vaccinated by the total cohort sizes per parish. Some of the years exceeded >100% vaccination coverage, which could be at least partly explained by population movement, i.e. individuals being vaccinated in a parish other than their registered living parish.

In **Chapter II**, vaccination coverage per SEG was estimated similarly. In brief, vaccination coverage was estimated by dividing the annual number of vaccinated per SEG by the total cohort size per SEG and parish. Information on the SEG of the vaccinated individuals was included in the digitized vaccination records. The total cohort sizes of each SEG per parish were estimated using two datasets: 1) cohort sizes from the population census tables and 2) occupational census records of men to estimate the distribution of the SEGs per parish. In case there were major differences in the birth rates of the SEGs, I checked the resulting vaccination coverages by using occupational data of women and children from the same census tables that contained data on the men. Further details are included in **Chapter II**.

2.3 Statistical analyses

All statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria) (R Core Team, 2020). This thesis used a variety of statistical models, including general linear models (GLMs) (**Chapter I**), generalized linear mixed models (GLMMs) (**Chapters I, II and III**), wavelet analysis (**Chapter I**), threshold models (**Chapters I and II**), generalized additive mixed models (GAMMs) (**Chapters I and II**), the Cox proportional hazard (CPH) model (**Chapter III**) and competing risks analysis (**Chapter III**). Further details can be found in the methods sections of each chapter. All linear model assumptions were checked with the function 'simulateResiduals' of the R package 'DHARMA' (Hartig, 2020) and the statistical 'significance' of predictor variables was quantified using both p-values (**Chapters I and III**) and with the model selection approach based on the second-order Akaike information criterion (AICc) values (**Chapters I, II and III**) (Burnham et al., 2011; Burnham et al., 2002), with the function AICc of the R package 'MuMIn' (Barton, 2020). In brief, the models are ranked based on their AICc value, and the best-fitting model is indicated by lower AICc, models within 4 Δ AICc are considered plausible, and increasingly implausible up to 14 Δ AICc after which they are implausible (Burnham et al., 2011; Burnham et al., 2002).

To account for the fact that people are clustered into parishes, I included parish identity as a random intercept in the models of all chapters. In **Chapters I and II**, some of the models also controlled for temporal autocorrelation following Woods (Woods, 2017) by including standardized year as an autoregressive factor of order 1

(corAR1). For **Chapters I and II**, all model residuals were checked for temporal autocorrelation ($ACF < 0.1$) using function ‘acf’ in the package ‘stats’ (van Panhuis et al., 2013).

In **Chapter III**, to avoid confounding grandmother survival and socio-economic status, the models controlled for childhood socio-economic status as previous research on this population had found differences in women’s life-history traits between social classes (Pettay et al., 2020; Pettay et al., 2007). I classified social class as a 3-level variable as described above and according to an earlier study on this population (Pettay et al., 2007). **Chapter III** models also controlled for the number of siblings to avoid confounding the number of grandchildren with grandmother effects, and both birth parish and birth cohort were included as a random intercept, to control for spatial and temporal clustering. In the survival models mother identity was nested within birth parish to account for siblings from the same family.

3 Results & Discussion

3.1 Characteristics of the vaccination campaign and the impact of the vaccination law

In **Chapter I**, I explored the characteristics of Finland's first vaccination campaign and the impact of the 1883 vaccination law on vaccination coverage. I showed that children were vaccinated at any age without a lower age limit, unlike in more contemporary societies, where the recommended age for smallpox vaccination was 1 year (Kempe, 1960). There is a possibility that vaccination was at least partially ineffective for some of the infants vaccinated before the age of 3 months due to maternal blunting (Zimmermann et al., 2019). I also found significant variation in vaccination coverage between the study parishes, which could have several explanations. Especially rural communities could have difficulties accessing vaccines or, with the management of the vaccination campaign, have less motivation to vaccinate, or be more prone to vaccine hesitancy (Thomas et al., 2019; Wagner et al., 2020). These local differences in vaccination coverage remained after the introduction of the vaccination law, implying that there were persistent parish-level differences in vaccination coverage. Moreover, it is possible that there were regional differences in the implementation of the vaccination campaign, for example, some undigitized vaccination records from the Helsinki area suggest that some cities may have vaccinated twice a year instead of just once. Thus, future studies should explore the reasons behind these urban-rural differences in vaccination coverage and vaccination campaign management and whether the 1883 vaccination law had more of an impact on vaccination coverage in poorly accessible rural areas than in better-connected cities.

In contemporary societies, it has been highly debated (Bardosh et al., 2022; Maquiling et al., 2023; Mello et al., 2022; Mills et al., 2022), whether mandatory vaccination has been considered a tool to combat declining vaccination coverage. In **Chapter I**, I show an abrupt increase in vaccination coverage occurring simultaneously with the introduction of the 1883 vaccination law, which persisted for at least for 17 years. This result is confirmed in **Chapter II**, with a larger dataset, as well as in contemporary populations (France, Italy, and the US) for several vaccines, including measles, mumps and rubella (MMR), varicella, and pertussis

(Gori et al., 2020; Lévy-Bruhl et al., 2019; Seward et al., 2002). These findings in **Chapters I** and **II** indicate that a vaccination law can stop a declining trend in vaccination coverage and suggest that the increases observed now in contemporary societies might persist in the long term.

3.2 The impact of the vaccination law across socio-economic groups (SEGs)

In **Chapter II**, I investigated to what extent the vaccination law was able to increase vaccination coverage in all SEGs. I showed that the 1883 vaccination law succeeded in improving population-level vaccination coverage, but its impact varied between the SEGs. The middle SEG showed the most improvement in vaccination coverage, where coverage increased by 35% and hence likely drove the population-level result. The high SEGs had high vaccination coverage that remained above the 80% herd immunity threshold for smallpox both before and after the vaccination law. The low SEG had the lowest vaccination coverage at 26% before the law, increasing only to 32% after the law.

In contemporary societies, the variation in vaccination coverage between SEGs varied between studies. Some studies, e.g., in the UK, Ireland, the Netherlands, Greece and Australia, reported high infant MMR vaccination coverage in wealthy or highly educated parents (Danis et al., 2010; Hungerford et al., 2016; Jessop et al., 2010; Pearce et al., 2015; Van Lier et al., 2014), but other studies found no association between parental income and/or education level (Poethko-Müller et al., 2009; Wallby et al., 2013) and some found the opposite trend (Anello et al., 2017; Barata et al., 2012). Hence, the variation in infant vaccination coverage between SEGs seems complex.

Multiple factors can explain how low SEGs can end up lagging behind in infant vaccination coverage. If lower SEGs have barriers to accessing vaccines, this could be explained by the lack of infrastructure to reach all citizens. Another barrier can be a lack of information about the benefits of vaccines, which can lead to higher hesitancy towards vaccines among the lower SEGs (McKinnon et al., 2021; Prickett et al., 2021; Sacre et al., 2022; Urrunaga-Pastor et al., 2021). In 19th century Finland, the differences in infant vaccination coverage between SEGs can result from both a lack of resources, such as vaccines and vaccinators, available to the vaccination campaign and/or increased vaccine hesitancy in the lower SEGs. Since I observed significant differences in vaccination coverage between the study parishes, it would be interesting to further investigate these spatial differences, e.g., whether there is a clustering of low vaccination coverage predominantly in parishes with low average socio-economic status, how the differences in vaccination coverage impacted the

burden of smallpox mortality between the parishes and whether the vaccination law changed this dynamic.

3.3 Family relationships and incentives to vaccinate

In **Chapter III**, I tried to identify family factors that could affect vaccination coverage. In historical Finns, grandmothers have an important role in family dynamics (Pettay et al., 2007). Hence, I investigated if grandmothers improved grandchild (i) survival from childhood infections and (ii) vaccination coverage. Maternal grandmothers improved the all-cause survival of their grandchildren, which was at least in part mediated by a decrease in mortality due to smallpox, pulmonary infections, and diarrhoea. The increased survival was not mediated via vaccination since the grandmother's presence did not alter the coverage of the smallpox vaccine, the only vaccine that existed at that time.

Before modern medical care, grandmothers helped with food provisioning along with improved hygiene and knowledge, for example, on the early symptoms of these diseases could have been important in decreasing mortality from infectious diseases (Tanskanen et al., 2018; Moring, 1998; van Wijhe et al., 2016). Although historical incidence data for this population is not available, ideally, I would have liked to test whether grandmothers decrease case fatality rates (i.e., the proportion of diagnosed people who die from a specific cause of childhood infection in grandchildren would be useful) to disentangle exposure to the disease from the children who got sick but recovered.

Contrary to my expectation, grandmothers did not change the measles-mediated mortality of grandchildren. I believe that the negative measles result can occur, either because grandmothers could have been less successful at protecting against measles due to its higher mortality risk (de Vries et al., 2012; Karp et al., 1996) or because providing care and nutrition was a less successful strategy against measles infection (Mina et al., 2019). The grandmother effect could also have been diminished by underreporting of measles deaths, as the immunosuppressive mechanism of measles leaves individuals at risk of dying from other infections, which would not have been recognised as measles deaths.

Finally, contrary to my expectations, I found no evidence that grandmothers improved vaccine uptake or encouraged earlier vaccination of their grandchildren, meaning that the benefits of grandmother presence on smallpox-related mortality were not mediated via vaccination. In contemporary populations, studies have shown the opposite result, i.e., grandmothers promote vaccination (Atiyeh et al., 2005; Li et al., 2014; Mixer et al., 2007). The difference between historical and contemporary societies may occur because these societies have different incentives for vaccination.

At the time, the smallpox vaccine was a novel innovation (Jenner, 1798). The early versions of the vaccine occasionally had serious side effects, which could have raised concerns about vaccine safety. Moreover, grandmothers in 18th and 19th century Finland likely were aware of the severe risks of infectious diseases, but had not yet experienced all the benefits of vaccination campaigns, unlike grandmothers during the 20th century (Henderson et al., 1999; Manzoli et al., 2007; Suthar et al., 2022; van Wijhe et al., 2016). There is also a possibility that grandmothers were more important to the vaccination efforts in the early 1800s, after the rollout of first vaccines, but I found no effect of grandmother presence on vaccine uptake before or after the law. Thus, grandmother help may be more complex than previously assumed.

3.4 Strengths and limitations of the project

These historical data allowed long-term monitoring of the spatio-temporal dynamics of vaccination coverage and investigate the impacts of the vaccination law, something that is not yet possible with contemporary data. These data are rarely available but important for quantifying effective strategies in improving and maintaining high vaccination coverage and contributing to the control of infectious diseases on the long-term. Moreover, the data on the socio-economic status I used in **Chapters II** and **III**, are rarely collected and thus often unavailable from contemporary societies due to ethical reasons.

This thesis has several limitations. During the 19th century, Finland's vaccination campaign against smallpox likely improved in distribution and management over time, which may have improved vaccine uptake besides the vaccination law. While there may have been sudden organizational changes in the vaccination campaign, historical records do not indicate such changes in the management (Björkstén, 1908). The vaccination data was also limited to two to ten rural towns per study. Vaccination campaigns may have been managed differently in cities vs. rural parishes, and it is unclear to what extent the characteristics of the vaccination campaign and the response to the vaccination law described in this thesis apply to other settings.

My estimates for the vaccination coverage also include children of temporary travellers from other parishes, which at least partly explains the datapoints exceeding >100% vaccination coverage. Thus, I may have overestimated the success of vaccination campaigns both before and after the vaccination law. All historical data also include human error and varying levels of detail and precision for example in identifying causes of death, on the population census or in the vaccination records, as these data have been recorded by local priests who were responsible for a wide variety of tasks they were not always qualified for.

4 Summary/Conclusions

In this thesis, I investigated three separate characteristics of Finland's first vaccination campaign against smallpox: **(I)** mandatory vaccination, **(II)** socio-economic differences in vaccination coverage and **(III)** the impact of family networks on vaccination coverage and infection-mediated infant mortality. In **Chapter I**, I described the key characteristics of the vaccination campaign, the long-term impact and spatiotemporal dynamics of the vaccination law on vaccination coverage. Next in **Chapter II**, I tested whether this law was able to increase and equalize infant vaccination coverage across socio-economic groups. Finally, in **Chapter III**, I investigated the effect of grandmother presence on all-cause and cause-specific mortality of grandchildren, and whether improved survival from smallpox was mediated via promoting vaccination.

Many factors can simultaneously affect vaccine uptake, which is why a diverse range of strategies to increase vaccination coverage should be considered, including training medical professionals and improving communication about the benefits of vaccines to the public. If implementing vaccination laws becomes necessary, it is important that the communication about these laws is clear and consistent. There is also a risk that without careful implementation vaccination laws can reinforce existing inequalities between the socio-economic groups. The findings in **Chapters I and II** indicate that vaccination laws have potential to be one of the long-term tools used to work towards the elimination of childhood infections, but other strategies are needed to reach the communities with the lowest vaccination coverage, including information campaigns and easier access to vaccines, for example, allowing time off from work or physical access to vaccination events.

Contrary to my expectations, although grandmothers did improve the survival of their grandchildren, which was mediated via improved survival from infectious diseases, there was no impact of grandmothers on vaccine uptake. Grandmother help is likely multifaceted, for example, grandmothers hesitate to recommend vaccines they had no previous experience with, but more likely to recommend vaccines they were familiar with, and this requires further study.

These findings imply that a multitude of factors can have an impact on vaccine uptake. In this thesis, I identified some strategies that succeeded in improving

vaccination coverage (and some that had no effect). I show that while some strategies, such as vaccine mandates are helpful, on their own they are insufficient to protect all infants. Therefore, additional effective strategies to improve vaccine uptake require further investigation. As infectious diseases are a major public health concern, finding effective vaccination strategies to combat the burden of diseases on human health is as important now as it was at the beginning of the smallpox vaccination campaign over 200 years ago.

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