Multigenerational Effects of Smallpox Vaccination

Lazuka, Volha; Jensen, Peter Sandholt

2021

Document Version:
Other version

Lund Papers in Economic History

No. 232, 2021

Multigenerational Effects of Smallpox Vaccination

Volha Lazuka & Peter Sandholt Jensen

DEPARTMENT OF ECONOMIC HISTORY, LUND UNIVERSITY

MULTIGENERATIONAL EFFECTS OF SMALLPOX VACCINATION

Volha LAZUKA* and Peter Sandholt JENSEN**

This version: 13 December 2021

Abstract

This paper aims at finding whether vaccination in childhood is an important source of improved health over the life cycle and across generations. We leverage high-quality individual-level data from Sweden covering the full life spans of three generations between 1790 and 2016 and a historical quasi-experiment – a smallpox vaccination campaign. To derive the causal impact of this campaign, we employ the instrumental-variables approach and the siblings/cousins fixed effects. Our results show that the vaccine injection by age 2 improved longevity of the first generation by 14 years and made them much wealthier in adult ages. These effects, with the magnitude reduced by two thirds, persisted to the second and the third generation. Such magnitudes make vaccination a powerful health input in the very long term and suggest the transmission of environmental beyond genetic factors.

Keywords: intergenerational transmission of health; smallpox vaccination; instrumental-variables; Sweden.

JEL codes: I12; I15; I18; I38; J24; E24; N43.

* Corresponding author: vola@sam.sdu.dk, University of Southern Denmark and Lund University; ** Linnaeus University and University of Southern Denmark

I. Introduction

Health inputs in childhood appear to strongly determine human capital and success throughout the life cycle, a finding adhering to both historical and contemporary populations (Almond et al., 2018). The importance of these inputs becomes even more critical if intergenerational transmission of health is considered. According to recent evidence, a child can expect to inherit up to a fourth of their parents' health capital (Halliday et al., 2018). This channel of intergenerational heritage may be the strongest of socio-economic channels as the long-documented associations between socio-economic statuses and earnings are much smaller (e.g., Lindahl et al., 2015). If this is the case, public health investments may become a source of diminishing health and income inequality in the very long term. Yet, current research is very far from proposing clear policy recommendations. What is not known to date is whether intergenerational health links are instead not the product of a mere comparison of individuals with healthier and weaker genes (cf. van den Berg et al., 2019), and accordingly, whether exogenous health inputs can indeed induce a causal chain of improved health. Moreover, previous research has measured health broadly that, due to its complexity, does not suggest possible paths for intervention.

In this study we aim for an argument that a positive health shock in the form of vaccine is an important source of improved health over the long run and across generations. To fill in the gap in the existing literature, we investigate whether the rollout of smallpox vaccination in Sweden enabled individuals to live longer and be wealthy as adults, and whether consecutive generations were healthier and better off. To carry out our investigation, we leverage unique historical individual-level data and focus on the cohorts exposed to the

vaccination campaign in early childhood, which marks the start of the causal chain across their lives and generations. This campaign was implemented in such a way that we could exclude the influence of unobservable factors based on an instrumental-variables strategy and thereby derive the plausibly causal estimates. Our core outcome is mortality which is the ultimate output of the health production function; the time depth of the data – spanning from 1790 until today – allows us to trace the effects of smallpox vaccination for the full life cycle of at least three generations. Not only this, but we are also able to examine through what mechanisms, biological and/or socio-economic, the initial and intergenerational vaccination effects evolve.

We find that smallpox vaccination induced gains in survival and affluence not only for the first generation but also for the second and the third generation. In absolute terms, this positive shock to the individual's health adds 14 years of life on average in adulthood of the first generation. Indeed, while mortality from smallpox is reduced the most, we find strong vaccination-induced negative effects on mortality from other causes. For the subsequent generations, such a gain amounts to 5 and 4 years of life which is around a third of the (grand)-parental gain. We also find that, due to vaccination in early life, individuals belonging to the first generation were more likely to attain higher socio-economic status and vaccinate their own children in adulthood. Their children and grandchildren were also more affluent. Yet, the main channel through which these descendants inherited benefits of the first generation's vaccination status is the direct effects of health and acquired immunity, according to the causal mediation analysis. Our results are similar across specifications

applying several empirical approaches of causal inference such as controlling-for-observables, instrumental-variables, and siblings(cousins)-fixed effects.

Our paper contributes to four strands of literature. First, economic historians have suggested that either resistance (through better nutrition and wealth) or exposure to disease (through changes in pathogens or public health measures) might underlie the general mortality decline (see, for instance, a review in Floud et al., 2011). A typical approach has been to plot country wide or regional time series of smallpox mortality and based on these determine informally whether a decline is observed at the time of the introduction of the vaccine. In a recent study, Ager et al. (2017) used a difference-in-differences approach and established that smallpox vaccination in Sweden led to a large initial decline in infant mortality. We confirm the findings with the individual-level data and contribute by taking a cohort approach and measuring the impact of smallpox vaccination across the full life cycle of the affected cohorts.

Second, as mentioned, a rapidly growing literature in applied economics has recently shown that negative environmental shocks and medical interventions in early life have large causal impacts on later-life health and earnings (Almond and Currie, 2011; Almond et al., 2018). Reforms that affected the spread of infectious disease – such as isolation hospitals, tuberculosis dispensaries or quality midwifery – or provided treatment – such as the introduction of sulpha antibiotics – have been found to have short- and long-term effects (Egedesø et al., Forthcoming; Lazuka, 2018; Lazuka, 2019, 2020). As far as vaccination is concerned, Bütikofer and Salvanes (2020) found the persistent positive effects of tuberculosis campaign on a variety of the outcomes of the affected cohorts and their children. Another

study has not found any long-term consequences of polio vaccination (Serratos-Sotelo et al., 2019). We contribute to this literature by exploring the vaccination campaign that is the first known public health initiative worldwide and an intervention with limited coverage in previous research.

Third, our knowledge on whether health shocks for one generation determine the outcomes of the subsequent generations is extremely scarce. Most of the work produced associations, including those for the life spans (e.g., Ahlburg, 1998; van den Berg et al., 2019). Yet, there are several studies that attempt to derive the causal impacts of health transmission by relying on different sources of exogenous variation. The only study prior to ours to look at a health shock specifically across generations is Cook et al. (2019) who have studied the impact of the 1918 influenza pandemic across two generations. Another study has tested whether the negative effects of the in-utero exposure to the abolishment of the alcohol ban are present for the second generation (Nilsson, 2017). The other work establishes a strong correlation between children's and own mother's low birth weight by comparing mothers who are sisters (Currie and Moretti, 2007). A study using adoptees investigates the relative importance of biological and adoptive parents in later-life health (Björkegren et al., 2020). Our study is the first ever to trace and find the effects of a positive health shock over the full life cycles of three generations.

Finally, live vaccines have been proposed to have non-specific effects meaning that they will offer protection against other diseases than the specific disease that they are designed to prevent (see Benn et al., 2016 for a review). For instance, Rieckmann et al. (2017) have exploited the phase out of the smallpox and BCG vaccines in Denmark as a source of

exogenous variation in child health. They found that school children that had received vaccines experienced lower mortality compared to those who did not get the vaccines, in an environment in which smallpox had practically been eradicated. The existence of such effects has been recently supported by the findings on the measles vaccination (Fisker et al., 2014). We contribute to this literature with the findings based on the consequences of the vaccine that are historical yet last for two centuries until today.

II. Background on Smallpox Vaccination in Sweden

In 1798, Edward Jenner published a book which described the method of vaccination against smallpox. The book detailed how he had first vaccinated a boy with cowpox. Eight weeks later Jenner inoculated the boy with smallpox. As there was no reaction, the conclusion drawn by Jenner that the vaccine was effective. Vaccination reached Sweden a few years later and was first mentioned on 7 December 1801 by the Medical Board of Sweden. The first vaccinations were carried out at the end of 1801 by Eberhard Zacharias Munch of Rosenschöld. From 1803, it was official policy that the Inoculation House of Stockholm should keep fresh vaccine matter and by the summer of the same year, most physicians and surgeons had taken up vaccination.

The vaccination campaign that followed had several remarkable features that we exploited in the analysis. First, in 1804 every parish was instructed to appoint a vaccinator. From 1805, all church assistants had to learn to vaccinate, and this group were also the most common vaccinators. Available data for the 1810s suggest that more than 60 % of vaccinators were church assistants or church musicians. We will exploit this fact in our empirical analysis,

see below. Second, fees for vaccination were paid by the parents and in general they were either very low or not charged at all. Vaccination was free for the poor and covered by poor relief. This suggests that there should be no differences by social class in the practice of vaccination in the case of Sweden. In fact, this observation is confirmed in the data that we use in this paper. Finally, from March 1816, it became compulsory for all children below the age of two to be vaccinated. parents would have to pay a fine if children were not vaccinated. If parents could not pay the fine, they would face imprisonment on a diet of water and bread.

Before the introduction of vaccination, inoculation was used as a preventive measure against smallpox. Inoculation is a deliberate infection with smallpox (rather than cowpox) via the skin. Inoculation was introduced in Britain in 1721, but it was not until 1756 that it was first used in Sweden. The historical narrative suggests that inoculation never gained wide acceptance because of, for instance, the risk of dying from the procedure (Pettersson, 1912). Our data confirm that inoculation had low uptake in Sweden: only a dozen of parishioners was inoculated between 1760 and 1800.

Smallpox was the most common childhood disease in the pre-vaccination area, but its significance declined after the introduction of vaccination. Figure 1 presents mortality rates by cause of death aggregated into several large groups in the area under analysis in 1780–1920. Even though the share of unknown causes of death is the most substantial among all causes, the symptoms of the main infectious diseases were recognizable to the priests and the doctors, so these diseases were registered rather accurately (Bengtsson and Lindstrom, 2000). With this argument at hand, we observe that the influence of smallpox declined with the inception of vaccination. Yet, some children still died due to smallpox throughout the

whole 19th century. Other airborne infectious diseases, such as diphtheria, scarlet fever, whooping cough and measles, gained in terms of importance in the post-vaccination period. Importantly, child mortality exhibits clear spikes driven by infectious diseases. This points to the epidemic nature of the disease environment for the cohorts under analysis. What adds credibility to our case is that the levels and patterns of child mortality accord with those for the whole of Sweden (Hofsten and Lundström, 1976).

[Figure 1 is about here]

We further present our data (explained in detail below) on the uptake of vaccination by cohort. In particular, we plot the share of cohorts by vaccination status at the age of 2 and in later child ages in 1790–1825. Figure 1 shows that cohorts born in the beginning of the 19th century had relatively low uptake, but that uptake increased over the first two decades of the 19th century. Interestingly, mandatory vaccination of 1816 only leads to a modest increase in uptake among the small children. This would suggest that most of the uptake is associated with the availability of the vaccine rather than the mandatory law. It is, however, possible that the mandatory vaccination requirement sustained higher levels of vaccination for later cohorts. It is reassuring to observe that the share of vaccinated by age 2 among cohorts under analysis follows a pattern similar to development presented by Sköld (1996) on the vaccination rate for the whole of Sweden.

[Figure 2 is about here]

A question that naturally arises is why vaccination rates did not reach 100 % since vaccination was mandatory. The historical narrative suggests that the compulsory

vaccination law was a threat, which made most parents comply with vaccination (Pettersson, 1912). Yet, it is very difficult to find historical examples of fines being executed. Anti-vaccination opposition was very low in Sweden compared to other European countries, with the first known petition presented a half a century after the start of the vaccination. Nevertheless, some people were spreading the message that smallpox was a religious sin, and the local authorities were reluctant to bring in the policy and start a conflict with people who had religious reasons for refusing to vaccinate their children (Sköld, 1996). Another source of vaccine hesitance was that (false) stories about the negative consequences from vaccines were spread by vagabonds and beggars. Regarding parents who did not vaccinate their children, one local doctor classified cases as follows: 1) the loss in income due to the absence from work when taking a child to a vaccinator led parents to refrain from the option; 2) some parents derived pleasure from defying the law; 3) some parents had fears of the consequences of vaccination (Landsarkivet i Lund, 1805-1827). This suggests that the benefits of smallpox vaccination were not obvious for everyone, which points to its exogenous nature.[1]

[1] According to Hofsten and Lundström (1976), many contemporaries, including the leading economists, did not believe that mortality could be reduced at all during the 18th century and the first half of the 19th century. This substitution theory, to the effect that little would be gained by the elimination of one disease since other diseases would take over (and thus smallpox eradication can cause other diseases to gain prominence), was shared by several writers, including Malthus.

III. Data

Our data come from unique register-based datasets with longitudinal demographic and socio-economic information on the residents of 60 parishes in different parts of Sweden and on their descendants for the 18th–21st centuries. Figure 3 presents the parishes used in the analysis. We must admit that the parishes, whose residents' family histories were digitized and reconstructed, were not randomly selected into these datasets but were selected due to the high quality of the archival records. Nevertheless, it has been argued that together they represent the economic and health development of Sweden (Lazuka, 2017; Dribe and Quaranta, 2020; Edvinsson and Engberg, 2020). The resulting high-quality datasets – the Demographic Data Base (DDB) and the Scanian Economic-Demographic Database (SEDD) – are homogenous in terms of sources and structure and provide variables at the individual level in the same metrics across cohorts essential to this study. These variables include smallpox vaccination and infection status, various demographic events and population at risk, the cause of death (ICD-10), and occupation and socio-economic status (HISCO) at birth and throughout life.[2]

[Figure 3 is about here]

Out of these datasets, we extracted information based on several conditions. First, smallpox vaccination status should be accurately registered in the church books. Information on inoculation and vaccination against smallpox was usually recorded by the priest on several occasions, such as on the occurrence of this event, at birth, baptism, or migration. Yet,

[2] We used the most recent versions of the datasets: Bengtsson et al. (2021) and CEDAR (2021).

several parishes had few or no records which might point to under-registration or strong opposition to the vaccination. Second, data for the individuals living in the parish should exist for both the pre- and post-vaccination period because we intend to compare individuals within the same parish. Third, we extracted information on the individuals born between 1790 and 1820, and who form the first generation, together with information on their children, those born until 1865, and grandchildren, those born until 1910.[3] The upper threshold for the descendants corresponds to the last reproductive age of the latest born mother, so we can stick to the general definition of the generation. Additionally, these individuals should be born in the parishes, meaning that the earliest vaccination date is correct; to compare, settlers usually received the vaccination mark at the date of in-migration. In total, we could track the full life cycles of three generations – around 55,000 individuals, up until their death, out-migration, or the age of 100.[4]

Following the features of the vaccination campaign, our key variable is whether the individual (or one of their parents for the second generation, or one of their grandparents for the third generation) was vaccinated against smallpox by the age of 2 or never vaccinated.[5] As mentioned above, the law of 1816 required that children below age 2 should be vaccinated;

[3] For the first generation, we also exclude children of those born in 1790–1820. The length of this generation roughly equals to the mean age difference between parents and children.

[4] Only a few individuals in our sample pass this upper age threshold.

[5] The vaccination mark identified smallpox vaccination for 99.9% of the individuals with such a mark. For the rest, additional information for the mark allowed us to identify the following: immunity to smallpox, vaccination and immunity, or no vaccination, which we further exploited in analysis.

in line with the historical narrative, being vaccinated in the first years of life is most common after 1801, with the median age among the eventually vaccinated equal to 2.04 years. Our choice of the key variable was also motivated by additional empirical reasons. While we observed that there were individuals who received a vaccine injection at older ages, this group could suffer from a selection problem. As an illustration, if we choose the age of 5, around 30 % of the cohort died by this age for the study period forming the potentially selected group of survivors.[6] Another reason is that the lower age threshold the more ages we could cover for the first generation because only the follow-up after the threshold is to be analyzed to avoid an immortal time bias (Suissa, 2008).

The data also allowed us to construct various background characteristics of the individual, and we have found no evidence of potential selection into smallpox vaccination for the first generation. Figure in Appendix A presents the results of this analysis. Among the main characteristics potentially pointing to selection into smallpox vaccination, we considered those related to the wealth of the family such as the father's socio-economic status (measured with HISCLASS) and the mother's marital status, to the health status of the family such as the proportion of siblings dead, and to parenting such as whether the older sibling died due to an external or an unknown cause. Our finding of no significant differences across these variables accords with the fact of low or no costs associated with the vaccine, and with evidence from Sköld (1996) on the absence of significant correlations between

[6] That said, if we follow up individuals after age 15, we find vaccination effects on the hazard of death in adulthood and old ages being close to those presented in the main body of the paper.

similar variables with the vaccination rates across the regions of Sweden. In line with the fact that vaccination did not face opposition in Sweden, we also find that the vaccination status of the parents is not associated with the probability to vaccinate the child. Given the features of the vaccination campaign, what came as no surprise is that the most important variable accounting for most of the variation in the individual treatment status is the year of birth. Parish-of-birth is another strong predictor that points to local rather than to individual-level determinants.

We argue that the date of vaccination in our dataset is unlikely to suffer from severe measurement error. On the one hand, individuals had the vaccination marks in both catechetical and examination registers, i.e., at the occurrence of the demographic events or during regular censuses. This ensures that those who had a vaccine shot at some point in their life appear in our list of the vaccinated persons. In support of this statement, as shown in Figure in Appendix A, individuals in vaccination treatment groups are evenly distributed across seasons or month of birth. On the other hand, the exact date of vaccination may be somewhat imprecise, especially for those who were vaccinated after baptism, close to the age of 2. For instance, Dribe and Nystedt (2003) have suggested that the changing frequency of vaccinated children in the first post-vaccination years, which we also observe in our sample, might point to the inaccuracy of the exact age of vaccination. We have already addressed this potential problem by excluding children vaccinated after the age of 2 and/or not born in parishes. Nevertheless, for the sake of external validity we additionally checked whether those excluded are different by the baseline characteristics and found no indication for this (available upon request).

IV. Empirical Strategy

a. Controlling-for-Observables Approach

Both the features of the data and the phenomenon under study encouraged us to choose duration models with time-dependent effects for the analysis. First, since we are interested in analyzing complete life histories, all available observations within the parishes should be considered, including censored (i.e., permanently out-migrated) and return cases. Second, with 100 years of life as the age horizon, modelling an underlying survival function is demanding; as a merit, the proportional hazards model that we use leaves it unspecified, yet allows us to obtain it a-posteriori. Third, following the early-life epidemiological literature stressing the cumulative or interactive character of the early-life health inputs, we should allow the effect of smallpox vaccination to change across ages, and a proportional hazards model could easily incorporate such changes (Verweij and van Houwelingen, 1995). Finally, the cause-specific hazards are also of interest, which we modeled by treating events due to competing causes as censored observations. In doing this, the approach by Lunn and McNeil (1995) was applied; in particular, we stacked the events with as many rows as there were causes of death of interest, let each of the cause exercise its own time-dependent effect, and fitted a model stratified by cause.

Our aim is to derive the plausibly causal estimates of the smallpox vaccination by age 2 on the hazard of death of the first generation and their children and grandchildren (second and third generation) across their life cycles. Free and quick access to the vaccine as the main feature of the campaign together with our finding that there was no risk of self-selection

into the treatment suggest that we could rely on the controlling-for-observables as our baseline empirical strategy. Given this, our baseline specification is as follows:

$$\ln(h(t)) = \beta_1 \text{vaccinated}_i + \beta_2 \text{vaccinated}_i \text{ x } \ln(t) + \mathbf{X}_i + \varepsilon_i \quad (1)$$

where $\ln(h(t))$ is a natural logarithm of the hazard of death at age t, vaccinated_i is a dummy equal to 1 if the individual (or any of the parents for the second generation, and any of the grandparents for the third generation) is vaccinated against smallpox by the age of 2, and $\text{vaccinated}_i \text{ x } \ln(t)$ is an age-dependent effect of being vaccinated by the age of 2, and $\boldsymbol{X}_i$ is a vector of covariates.

Among $\boldsymbol{X}_i$, our baseline specification (1) includes linear and squared terms for the year of birth (centered in 1801) and parish-of-birth fixed effects. The former was added to partial out the influence of a deterministic trend in the hazard of death, thereby keeping any discontinuous changes in the estimate of the smallpox vaccination. The place of birth is an important predictor of the probability of being vaccinated in early life. Hence, adding parish dummies allowed us to exclude their influence as well. Importantly, the vector of parental (grand-parental) covariates, from the mother and the father (from two grandmothers and two grandfathers), was added as only controls for the second (third) generation, because the individual's own background characteristics rather represent intergenerational mechanisms. As an opportunity, smallpox vaccination could influence both demographic and socio-economic outcomes of the first generation that we will also study; if this is the case, parental characteristics or even their own year of birth should not be fixed (VanderWeele, 2011). The start of the follow up was the age of 2 for the individuals belonging to the first generation

and the age of 0 for further generations. All generations were followed until death, outmigration, or the age of 100.

b. IV Approach

Even with no indication of selection effects, when we rely on controlling-for-observables strategy, we cannot deny that there might be unobservable factors associated with the decision to vaccinate the child, for instance, trust or own experience of sickness with smallpox. To account for the influence of these omitted factors, the IV approach was applied, in particular, a 2-stage residual inclusion method that is applicable to the duration models (Terza et al., 2008). In the case of duration models, the IV strategy helps to account for the problem of omitted variables and measurement error in the smallpox vaccination indicator, and it also relaxes the assumption of random censoring (MacKenzie et al., 2021). The knowledge of the vaccination campaign provided an instrument to us, such as the number of church assistants in the parish. The equations estimated in two stages were the following:

$$\ln(\text{vaccinated}_i = 1) = \alpha_1 + \alpha_1 \text{church\_assistants}_{pt} + \mathbf{X}_i + \nu_i \quad (2)$$

$$\ln(h(t)) = \beta_1 \text{vaccinated}_i + \beta_2 \text{vaccinated}_i \times \ln(t) + \mathbf{X}_i + \beta_3 \widehat{\nu}_i + \varepsilon_i \quad (3)$$

where in the first stage the logistic probability of being vaccinated, $\ln(\text{vaccinated}_i = 1)$, is estimated as a linear function of the number of church assistants in the parish of residence of the individual in the first two years of life together with $\boldsymbol{X}_i$ that are parish-of-birth fixed effects and a linear and a squared term of the year of birth, and the individual's residuals from this equation, $\widehat{\nu}_i$, are saved. Maximum likelihood estimation of the logistic regression in the first stage is advised as opposed to a least squares estimation due to a binary nature

of treatment, like in our case, for which a proper model for a treatment is a location shift model (Tchetgen Tchetgen, 2014). In the second stage, we added the residuals saved from the first stage to the same specification as in (1) and estimated the effect of interest.[7]

c. Validity of the Instrument

Figure B.1 in Appendix B presents the panel of church assistants for 1790–1825 that we used in the analysis. Particularly useful were detailed data on main and secondary occupations of the individual in our datasets. To obtain a current number of available church assistants in the parish, we counted all adults occupied permanently or temporarily as church assistants and church musicians. While some may argue that vaccination was rather provided at the level of the pastorate, which administrated one or several parishes, we found that treatment is predicted very poorly if church assistants are counted at these larger geographical areas. The number of church assistants was set to null for the years before 1801, because these people did not participate in the vaccination. To validate these series, we also used parish vaccination reports sent to the state health board, Collegium Medicum (Riksarkivet, 1802-1812).

The obtained series of church assistants exercises a strong effect on the probability of being vaccinated against smallpox for the cohorts under analysis (see Table in Appendix B). In particular, one unit increase in the number of church assistants leads to an increase by

[7] In addition to including a residual, Tchetgen Tchetgen (2014) also recommend adding an interaction term between a residual and an instrument. Inclusion of this interaction provides results identical to those reported in the main body of the paper.

9.1 % in the odds of being vaccinated against smallpox below age 2. The probability of being vaccinated by age 2 increases from 40 to 47 % within the range of the number of vaccinators (see Figure B.2 in Appendix B). This effect is statistically significant at a 1 % level, and the effect's Lagrange multiplier Chi-squared test statistics is 11.19, implying that the instrument is strong, and we could use it in our analysis. As can be seen, there were several parishes where no residing clergymen were observed, yet the baseline probability was rather high there. This is not surprising as many other people, including midwives, doctors, or high-class women, participated in the vaccination campaign against smallpox (Sköld, 1996).

Our choice to focus on church assistants and musicians as the only subgroup of vaccinators is to address the main assumption of the instrumental-variables approach – the exclusion restriction. This untestable assumption states that the instrument should affect the outcome, in our case survival probability, only by increasing the probability of being vaccinated against smallpox. Historical sources highlight that Church workers were trustworthy and literate yet lacking knowledge on medicine (Sköld, 1996). To perform vaccinations, being rather easy to implement, these clergymen were trained with the instructions, distributed by the state, and by the other vaccinators (Banggaard, 2002). As an illustration, a church musician was the first vaccinator in one of the southern parishes who assisted at choirs and vaccinated against smallpox within a secondary employment yet unlikely improved survival chances of the parishioners through other channels (Landsarkivet i Lund, 1805-1827). In the neighbouring parish, initially did a licensed midwife vaccinate children (Landsarkivet i Lund, 1785-1857). Although the means of preventing disease were very limited in the beginning of the 19th century, some were practiced by doctors, such as

cause-of-death counting (Lazuka et al., 2016) or by midwives, such as proper assistance at labour (Lorentzon and Pettersson-Lidbom, 2021).

V. Analysis

a. The Effects of Vaccination on Survival of Three Generations

We start by presenting the results for the effects of being vaccinated against smallpox by age 2 for the hazard of death across the life cycle of the first generation, from the models that only control for observables. Figure 4 presents the related estimates for the age-dependent vaccination status in early life.[8] Results first indicate that vaccinated individuals – compared to those never vaccinated – had a lower hazard of death at any point of their life (see Panel A). This advantage is equal to a 76 % lower hazard of death on average across the ages, and this effect is highly statistically significant (see Table C.1 in Appendix C for the estimates). The positive effect of smallpox vaccination is dynamic: it is lowest at the age of 2, the start of the follow up, and then declines at a reduced rate through the life. We translated this relative difference into the absolute one, such as the average life expectancy.[9] In adult ages alone – ages important for the subsequent generations – the vaccination-induced

[8] It can be argued that the restriction of the effect of smallpox vaccination to change in a linear dependence on ln(t) is too strong. In response to this, we experimented with more flexible forms of this effect by means of piecewise and flexible parametric models and have generally found that the Cox proportional hazard model with dynamic effects is an adequate approximation of the shape observed from the other models.

[9] To calculate the average expectation of life based on the estimates from Eq.1, we first estimated the baseline cumulative hazard function, calculated the scenario-specific hazard contributions and the survival function, and then computed the integral of the latter in the ages of interest (Finkelstein and Vaupel , 2009).

gain is 13.2 years in the expectation of life. Particularly appealing is the dynamics of the hazard by the cause of death between the treatment groups (see Panel B). It is mortality due to smallpox that is the lowest among the vaccinated against smallpox, the advantage present at any age. While the hazard of death declines because of vaccination due to any other cause, deaths prevented from infectious and respiratory diseases remain the most important driver of the changes in survival during child and adult ages.

[Figure 4 is about here]

We turn to the results for the second and third generation and display them in Figure 5 Panel A and B accordingly. Observe that we now analyze survival of the offspring starting from their birth. Both generations whose ancestor was vaccinated against smallpox by age 2 – as compared to those whose ancestors were never vaccinated – have relatively lower hazard of death through the life cycle. Strikingly, a hazard ratio for having a parent (a grandparent) vaccinated is similar between generations: it is equal to a relative advantage of at least 15 %, which is statistically significant at a 1 % level, for any of the subsequent generations. Yet, the dynamics of these effects from vaccination differs between generations.[10] As for the second generation, the effect declines throughout child and adult ages, so that the difference between the treatment groups disappears by the older ages. In contrast, for the third generation, the effect of grandparental vaccination is rather stable across ages. Together the

[10] In additional analysis, we have found that, when the shape of the effect is permitted to be flexible, the effect of the parental vaccination is negative through all ages and remains statistically significant at 5% level until the age of 30.

multigenerational effects of vaccination result in the gain of 3.4 and 3.6 years of life for the second and third generation respectively. As a final note, we have found that the effects are not different between the maternal and paternal side (available upon request).

[Figure 5 is about here]

We further present the results from the 2SRI regressions for the three generations in Figure 6 (see also Appendix D for the estimates). These results establish similar impacts of the smallpox vaccination across the life cycle as those obtained from the controlling-for-observable models, yet with a somewhat pronounced decline in the impact across generations. Individuals who belong to the first generation of treated with vaccination against smallpox versus never treated have 80 % lower hazard of death across ages, and this gain in adulthood alone is equivalent to 14.4 additional years. Individuals belonging to the second and third generation have 29 and 23 % lower mortality risk accordingly, which translate to a total life gain of 4.8 and 3.9 years. Reflecting this similarity, are the estimates for the residuals from the first stage, which are constructed to capture the impact of the omitted variables, close to 1 on a hazard ratio scale and statistically insignificant for all generations. These findings point to several conclusions. First, there appear to be no omitted variable bias in the controlling-for observables estimates. This goes in line with our previous observation of no significant correlation of the probability of being vaccinated against smallpox with the socio-economic and behavioral covariates of the individual. Second, the survival responses to vaccination are likely homogeneous: recall that the IV approach exploits only variation in the smallpox vaccination induced by the church assistants.

[Figure 6 is about here]

The magnitude of the multigenerational effects on longevity suggests the importance of environmental factors beyond genetics. A feature of the survival data provides multiple scales by which we might decompose the effects. Recall from the instrumental-variables estimates that the vaccination-induced gains equal to 0.21, 0.81 and 0.87 across the generations on a hazard ratio scale. These imply that further generations "inherit" 24 and 16 percent in terms of the reductions in mortality risk, accordingly. Turning to a gain in a life expectancy scale, smallpox vaccination adds 14.5, 4.8 and 3.9 across generations, giving 33 and 27 percent of the parental gain for the descendants. Any of these scales suggests that the size of health transmission is beyond genetics because the impact of genetic factors dies out geometrically: first cousins share 12.5 percent, and second cousins only share 3.125 percent.

b. The Effects of Smallpox Vaccination on Socio-Economic Outcomes

In addition to the benefits for the individual's health, smallpox vaccination, like any health input, could potentially affect their socio-economic and behavioral outcomes (Cunha and Heckman, 2007); precisely these have we found for the first generation (see Table 1). First, being vaccinated against smallpox by age 2 leads to higher socio-economic status in adulthood. More specifically, probability of attaining a high-class occupation, which is defined as farmers and higher classes, increases by 34 % due to vaccination in early life. Likewise, the probability of having non-manual occupation rises sharply. Second, vaccination impacted health behaviour. Individuals vaccinated in childhood were much more likely to vaccinate their own children, in particular, by at least 2 times. Ager et al. (2017) found that

the decline in infant mortality due to smallpox strongly influences fertility among those who were adults at the inception of the vaccination in Sweden. Yet, the outcomes are cohort-specific in our analysis, and we have not found any vaccination-induced fertility responses. The results for all outcomes are not different between the controlling-for-observables and the IV estimations.

[Table 1 is about here]

Inherited health traits could also lead to economic gains for the descendants (Heckman and Mosso, 2014), and our findings support this proposition for the socio-economic status as an outcome. The results are provided in Table 2. Due to the predecessors' vaccination, individuals belonging to the second and third generation have around 15 % higher risk of attaining high socio-economic status in adulthood, and these effects are similar between the controlling-for-observables and the IV estimations. If to relate these intergenerational effects to those for the first generation (i.e., to 34 % increase in the relative risk of high-class attainment), we find a share of 40 % in percentage terms for both generations. As with the survival effects, this share is too large to only embed genetic effects.

[Table 2 is about here]

c. Mechanisms of Intergenerational Transmission of Health

The outcomes of the first generation are mechanisms through which their vaccination status translated to children's and grandchildren's longevity. We formulated our a-priori expectations about possible influences of these outcomes by considering the context of the individuals under analysis. A child's health responses to the outbreaks of infectious disease

are commonly found to be a good predictor of later-life health in the past (Bengtsson and Lindstrom, 2000; Quaranta, 2014). While it is true that one study for the area under analysis has argued that the lack of breastfeeding practices (i.e. a behavioral factor) explains differences in infant health in one of the Northern parishes (e.g., Brändström et al., 2000), this work relied on a descriptive method. Conversely, Lorentzon and Pettersson-Lidbom (2021) have established that employment of licensed midwives, which is exogenous to the individual's outcomes and should compensate for the lack of early-life nurturing, had no impact on infant health until the inception of antiseptics. Besides, a child's parental or own adult's socio-economic status has been found to exercise no clear impact on their mortality (Bengtsson and Dribe, 2011; Dribe and Karlsson, 2021).

We further applied a causal mediation analysis to attribute the total mortality effects to the direct and indirect effects of vaccination. The proportional hazards model with a common outcome, like in our case, allowed for the use of the weighting approach proposed by Lange et al. (2012) to derive "natural effects".[11] In line with the above analysis, we modeled indirect effects through mediators that are the outcomes for the first generation, such as the year of birth, parental socio-economic status, and own vaccination status by age 2. Table E.2 in Appendix E provides the estimates for the Cox proportional hazard model with constant effects of predecessors' vaccination status. In total, we have not detected any strong mediating effects, "natural indirect effects", with these factors. Apparently, it is either

[11] It is true that the causal inference in this part of analysis requires strong assumptions that become even less plausible the longer the age span to be analyzed. To address these, we added more covariates to the analysis, and it did not affect the results.

a direct transmission of health and survival (i.e., their genetic and/or environmental influences) or the impact of unaccounted mediators, as becomes clear with the strong and highly statistically significant "natural direct effects", which explains the effects of predecessors' smallpox vaccination status.

In relation to the direct effects of health, we could tentatively attribute the long-term effects of vaccination to acquired immunity (cf. Sørup et al., 2011). It became possible because people who got sick with smallpox were registered in the database before and after the inception of vaccination, and a large share of them went through this disease before age 2. In the analysis, we placed these individuals into a separate category and estimated its constant and age-dependent effect with Eq.1. Results are shown in Appendix F, and several of them worth mentioning. On the one hand, individuals who were infected with smallpox and survived past age 2 have a strong health advantage compared to individuals who were neither vaccinated nor infected. In childhood, this advantage becomes identical to the advantage of vaccination against smallpox. On the other hand, any differences in hazards of death between infected and counterfactual populations disappear in late adulthood. In total, a large portion of the vaccination effects in age 15–50 may indeed be related to acquired immunity.

d. Robustness Analysis

While we have applied an IV strategy and demonstrated the validity of beneficial effects of smallpox vaccination, it is possible that the assumptions of this strategy do not hold. We exploited several more opportunities to distinguish the impact of unobservable characteristics

from the variable of interest, such as the calculation of the potential strength of the unobservables and the placebo effects as well as first generation's mother fixed effects.

We applied a sensitivity analysis that does not rely on any assumptions on the nature of the underlying data-generating process – an analysis of the e-value that shows how robust the effect to potential unmeasured selection (VanderWeele and Ding, 2017). Figure G.1 in Appendix G presents the e-value and its lower 95%-CI for the effects of the first generation across the life cycle. These two measures suggest that all potential selection effects should be associated with both vaccination and survival by a hazard ratio of at least 4.5 (4.1) to kill the main effect of vaccination in ages 15-50. Because the understanding of these effects should be context-specific, we benchmarked and estimated the impact and the e-value of the early-life condition associated with misery, neglect and poor prospects in life – being born out of wedlock (Edvinsson et al., 2005).[12] Table and Figure G.2 in Appendix G reports these estimates. Indeed, they indicate that illegitimate children, in comparison to legitimate ones, carry on disadvantage in survival throughout childhood and adulthood. Yet, does the strength of this association amount to not more than 1.5 [95%CI: 1.2; 1.8] at the highest point of the hazard ratio scale. This implies that such a predictor is not able to eliminate the effect of smallpox vaccination.

The availability of generational links also allowed us to compare the outcomes within the groups of relatives. That is, we estimated the survival of first generation and their

[12] As we found in further analysis, neither of the other individual-level covariates have been associated with strong effects in childhood nor have they had any lasting consequences across the life cycle.

offsprings by comparing vaccinated and never vaccinated individuals within the same families. Such an extremely strict comparison should difference out any potential selection effects as it compares children who were born earlier than the vaccine became available to their luckier, later born, siblings. The only additional assumption to be made is that there was no differential parental treatment between children, otherwise these estimates embed parental responses. Appendix H presents the results of these analyses for three generations, where in Eq.1 we let the baseline hazard to be different for each group of siblings, first cousins and second cousins – accordingly to the generation analyzed. The results obtained tend to point to similar conclusions as above, both in patterns and sizes, although they become less precise.

VI. Conclusions

In this paper we investigated whether the rollout of smallpox vaccination in early life enabled individuals to live longer and be wealthy as adults, and whether their consecutive generations were healthier and better off. To carry out our investigation, we leveraged unique historical individual-level data from Sweden and focused on the introduction of smallpox vaccination in in 1801. The vaccination campaign was implemented in such a way that we could exclude the influence of unobservable factors based on an instrumental-variables strategy and thereby derive the plausibly causal estimates. Our core outcome is mortality, the ultimate output of the health production function, and the time depth of the data allows us to trace the effects of smallpox vaccination for the full life cycle of at least three generations. Not only this, but we were also able to examine through what mechanisms, biological and/or socio-economic, the initial and intergenerational vaccination effects evolve.

We found that smallpox vaccination induced gains in survival and affluence not only for the first generation but also for the second and the third generation. In absolute terms, the positive shock to the individual's health adds 14 years of life on average in adulthood of the first generation. Indeed, while mortality from smallpox is reduced the most, we find strong vaccination-induced negative effects on mortality from other causes. For the subsequent generations, such a gain amounts to 5 and 4 years of life which is around a third of the (grand)-parental gain. We also found that, due to vaccination in early life, individuals belonging to the first generation were more likely to attain higher socio-economic status, and that their descendants have higher socio-economic status. Yet, the main channel through which children and grandchildren inherited benefits of the first generation's vaccination status was the direct effects of health and acquired immunity, according to a causal mediation analysis.

Our findings have important policy implications. First, the evidence on that smallpox vaccination offers protection not only against smallpox, but also against other diseases, makes vaccination a powerful health intervention. Second, the fact that there are intergenerational health and economic benefits from vaccination suggests that the total benefits of smallpox vaccination were much larger than the existing literature would suggest. These findings also give room for reducing the inequality of opportunity. Whether these findings are applicable for other vaccines is beyond the scope of this paper but is an important topic for future research.

References

Ager, P., Hansen, C. W. and Jensen, P. S. (2017) 'Fertility and Early-Life Mortality: Evidence from Smallpox Vaccination in Sweden', *Journal of the European Economic Association*, vol. 16, no. 2, pp. 487–521.

Ahlburg, D. (1998) 'Intergenerational Transmission of Health', *American Economic Review*, vol. 88, no. 2, pp. 265–270.

Almond, D. and Currie, J. (2011) 'Human Capital Development before Age Five', in Card, D. and Ashenfelter, O. (eds) *Handbook of Labor Economics,* Amsterdam and New York, Elsevier, pp. 1315–1468.

Almond, D., Currie, J. and Duque, V. (2018) 'Childhood Circumstances and Adult Outcomes: Act II', *Journal of Economic Literature*, vol. 56, no. 4, pp. 1360–1446.

Banggaard, G. (2002) 'Sygdom og Sundhed: Offentlige Indgreb og Deres Virkninger i Sydsverige, ca. 1750-1894', *Lund Papers in Economic History*, vol. 76.

Bengtsson, T. and Dribe, M. (2011) 'The late emergence of socioeconomic mortality differentials: A micro-level study of adult mortality in southern Sweden 1815-1968', *Explorations in Economic History*, vol. 48, no. 3, pp. 389–400.

Bengtsson, T., Dribe, M., Quaranta, L. and Svensson, P. (2021) *The Scanian Economic Demographic Database, Version 7.2* (Machine-readable database).

Bengtsson, T. and Lindstrom, M. (2000) 'Childhood Misery and Disease in Later Life: The Effects on Mortality in Old Age of Hazards Experienced in Early Life, Southern Sweden, 1760-1894', *Population Studies*, vol. 54, no. 3, pp. 263–277.

Benn, C. S., Fisker, A. B., Whittle, H. C. and Aaby, P. (2016) 'Revaccination with Live Attenuated Vaccines Confer Additional Beneficial Nonspecific Effects on Overall Survival: A Review', *EBioMedicine*, vol. 10, pp. 312–317.

Björkegren, E., Lindahl, Mikael, 1967, Palme, M. and Simeonova, E. (2020) 'Pre- and Post-Birth Components of Intergenerational Persistence in Health and Longevity: Lessons from a Large Sample of Adoptees', *The Journal of Human Resources*, forthcoming.

Brändström, A., Edvinsson, S. and Rogers, J. (2000) 'Infant Mortality in Sweden; Creating Regions from Nineteenth-Century Parish Data', *Historical Methods*, vol. 33, no. 2, pp. 105–114.

Bütikofer, A. and Salvanes, K. G. (2020) 'Disease Control and Inequality Reduction: Evidence from a Tuberculosis Testing and Vaccination Campaign', *The Review of Economic Studies*, vol. 87, no. 5, pp. 2087–2125.

CEDAR (2021) *The Demographic Data Base, U20003* (Machine-readable database), http://dx.doi.org/10.17197/U20003.

Cook, C. J., Fletcher, J. M. and Forgues, A. (2019) 'Multigenerational Effects of Early-Life Health Shocks', *Demography*, vol. 56, no. 5, pp. 1855–1874.

Cunha, F. and Heckman, J. (2007) 'The Technology of Skill Formation', *American Economic Review*, vol. 97, no. 2, pp. 31–47.

Currie, J. and Moretti, E. (2007) 'Biology as Destiny? Short- and Long-Run Determinants of Intergenerational Transmission of Birth Weight', *Journal of Labor Economics*, vol. 25, no. 2, pp. 231–264.

Dribe, M. and Karlsson, O. (2021) 'Inequality in Early Life: Social Class Differences in Childhood Mortality in Southern Sweden, 1815–1967', *The Economic History Review*, n/a, n/a.

Dribe, M. and Nystedt, P. (2003) 'Information, trust and the diffusion of smallpox vaccination: The Case of Scania in Sweden, 1802–1835', *Scandinavian Economic History Review*, vol. 51, no. 1, pp. 9–28.

Dribe, M. and Quaranta, L. (2020) 'The Scanian Economic-Demographic Database (SEDD)', *Historical Life Course Studies*, no. 2.

Edvinsson, S., Brändström, A., Rogers, J. and Broström, G. (2005) 'High-Risk Families: The Unequal Distribution of Infant Mortality in Nineteenth-Century Sweden', *Population Studies*, vol. 59, pp. 321–337.

Edvinsson, S. and Engberg, E. (2020) 'A Database for the Future: Major Contributions from 47 Years of Database Development and Research at the Demographic Data Base', *Historical Life Course Studies*, no. 1.

Egedesø, P. J., Hansen, C. W. and Jensen, P. S. (Forthcoming) 'Preventing the White Death: Tuberculosis Dispensaries', *Economic Journal*.

Finkelstein, M. and Vaupel, J. W. (2009) 'Survival as a Function of Life Expectancy', *Demographic Research*, S8, no. 29, pp. 879–884.

Fisker, A. B., Hornshøj, L., Rodrigues, A., Balde, I., Fernandes, M., Benn, C. S. and Aaby, P. (2014) 'Effects of the Introduction of New Vaccines in Guinea-Bissau on Vaccine Coverage, Vaccine Timeliness, and Child Survival: An Observational Study', *The Lancet*

Global Health, vol. 2, no. 8, e478-e487.

Floud, R., Fogel, R. W., Harris, B. and Hong, S. C. (2011) *The Changing Body: Health, Nutrition, and Human Development in the Western World since 1700*, Cambridge, Cambridge University Press.

Halliday, T., Mazumder, B. and Wong, A. (2018) 'Intergenerational Health Mobility in the US', *IZA Working Papers*, vol. 11304.

Heckman, J. J. and Mosso, S. (2014) 'The Economics of Human Development and Social Mobility', *Annual Review of Economics*, vol. 6, pp. 689–733.

Hofsten, E. and Lundström, H. (1976) *Swedish population history. Main trends from 1750 to 1970.*

Landsarkivet i Lund (1785-1857) *Halmstads Kyrkoarkiv* (Sockenstämmans Protokoll och Handlingar), Halmstad, SE/LLA/13137/K I/1.

Landsarkivet i Lund (1805-1827) *Kävlinge Kyrkoarkiv* (Sockenstämmans Protokoll och Handlingar), Kävlinge, SE/LLA/13175/K I/1.

Lange, T., Vansteelandt, S. and Bekaert, M. (2012) 'A Simple Unified Approach for Estimating Natural Direct and Indirect Effects', *American Journal of Epidemiology*, vol. 176, no. 3, pp. 190–195.

Lazuka, V. (2017) *Defeating Disease: Lasting Effects of Public Health and Medical Breakthroughs between 1880 and 1945 on Health and Income in Sweden*, Doctoral Dissertation, Lund University.

Lazuka, V. (2018) 'The Long-Term Health Benefits of Receiving Treatment from Qualified

Midwives at Birth', *Journal of Development Economics*, vol. 133, July, pp. 415–433.

Lazuka, V. (2019) 'Early Life Assets in Oldest-Old Age: Evidence from Primary Care Reform in Early 20th-Century Sweden', *Demography*, vol. 56, pp. 679–706.

Lazuka, V. (2020) 'Infant Health and Later-Life Labor Market Outcomes: Evidence from the Introduction of Sulpha Antibiotics in Sweden', *The Journal of Human Resources*, vol. 55, no. 2, pp. 660–698.

Lazuka, V., Quaranta, L. and Bengtsson, T. (2016) 'Fighting Infectious Disease: Evidence from Sweden 1870–1940', *Population and Development Review*, vol. 42, no. 1, pp. 27–52.

Lindahl, M., Palme, M., Massih, S. S. and Sjögren, A. (2015) 'Long-Term Intergenerational Persistence of Human Capital: An Empirical Analysis of Four Generations', *The Journal of Human Resources*, vol. 50, no. 1, pp. 1–33.

Lorentzon, L. and Pettersson-Lidbom, P. (2021) 'Midwives and Maternal Mortality: Evidence from a Midwifery Policy Experiment in 19th-century Sweden', *Journal of the European Economic Association*, vol. 19, no. 4, pp. 2052–2084.

Lunn, M. and McNeil, D. (1995) 'Applying Cox regression to competing risks', *Biometrics*, vol. 51, no. 2, pp. 524–532.

MacKenzie, T. A., Martinez-Camblor, P. and O'Malley, A. J. (2021) 'Time dependent hazard ratio estimation using instrumental variables without conditioning on an omitted covariate', *BMC Medical Research Methodology*, vol. 21, no. 1, p. 56.

Nilsson, J. P. (2017) 'Alcohol Availability, Penatal Cnditions, and Log-Tem Economic Outcomes', *Journal of Political Economy*, vol. 125, no. 4, pp. 1149–1207.

Pettersson, A. (1912) 'Smittkopdödeligheten i Sverige under åren 1776-1875', *Hygiensk Tidskrift*, pp. 1–17.

Quaranta, L. (2014) 'Early life effects across the life course: the impact of individually defined exogenous measures of disease exposure on mortality by sex in 19th- and 20th-century Southern Sweden', *Social science & medicine (1982)*, vol. 119, pp. 266–273.

Rieckmann, A., Villumsen, M., Sørup, S., Haugaard, L. K., Ravn, H., Roth, A., Baker, J. L., Benn, C. S. and Aaby, P. (2017) 'Vaccinations against Smallpox and Tuberculosis are Associated with Better Long-Term Survival: A Danish Case-Cohort Study 1971-2010', *International Journal of Epidemiology*, vol. 46, no. 2, pp. 695–705.

Riksarkivet (1802-1812) *Collegium Medicum: Vaccinationsrapporter*, SE/RA/420606/E4.

Serratos-Sotelo, L., Bengtsson, T. and Nilsson, A. (2019) 'The long-term economic effects of polio: Evidence from the introduction of the polio vaccine to Sweden in 1957', *Economics & Human Biology*, vol. 35, pp. 32–41.

Sköld, P. (1996) *The Two Faces of Smallpox: A Disease and its Prevention in Eighteen- and Nineteenth-Century Sweden*, Umeå University, Umeå University.

Sørup, S., Villumsen, M., Ravn, H., Benn, C. S., Sørensen, T. I. A., Aaby, P., Jess, T. and Roth, A. (2011) 'Smallpox vaccination and all-cause infectious disease hospitalization: a Danish register-based cohort study', *International Journal of Epidemiology*, vol. 40, no. 4, pp. 955–963.

Suissa, S. (2008) 'Immortal Time Bias in Pharmacoepidemiology', *American Journal of Epidemiology*, vol. 167, no. 4, pp. 492–499.

Tchetgen Tchetgen, E. J. (2014) 'A Note on the Control Function Approach with an Instrumental Variable and a Binary Outcome', *Epidemiologic Methods*, vol. 3, no. 1, pp. 107–112.

Terza, J. V., Basu, A. and Rathouz, P. J. (2008) 'Two-stage residual inclusion estimation: Addressing endogeneity in health econometric modeling', *Journal of Health Economics*, vol. 27, no. 3, pp. 531–543.

van den Berg, N., Rodríguez-Girondo, M., van Dijk, I. K., Mourits, R. J., Mandemakers, K., Janssens, Angelique A P O, Beekman, M., Smith, K. R. and Slagboom, P. E. (2019) 'Longevity Defined as Top 10% Survivors and beyond is Transmitted as a Quantitative Genetic Trait', *Nature communications*, vol. 10, no. 1, p. 35.

VanderWeele, T. J. (2011) 'Causal mediation analysis with survival data', *Epidemiology (Cambridge, Mass.)*, vol. 22, no. 4, pp. 582–585.

VanderWeele, T. J. and Ding, P. (2017) 'Sensitivity Analysis in Observational Research: Introducing the E-Value', *Annals of internal medicine*, vol. 167, no. 4, pp. 268–274.

Verweij, P. J. and van Houwelingen, H. C. (1995) 'Time-dependent effects of fixed covariates in Cox regression', *Biometrics*, vol. 51, no. 4, pp. 1550–1556.

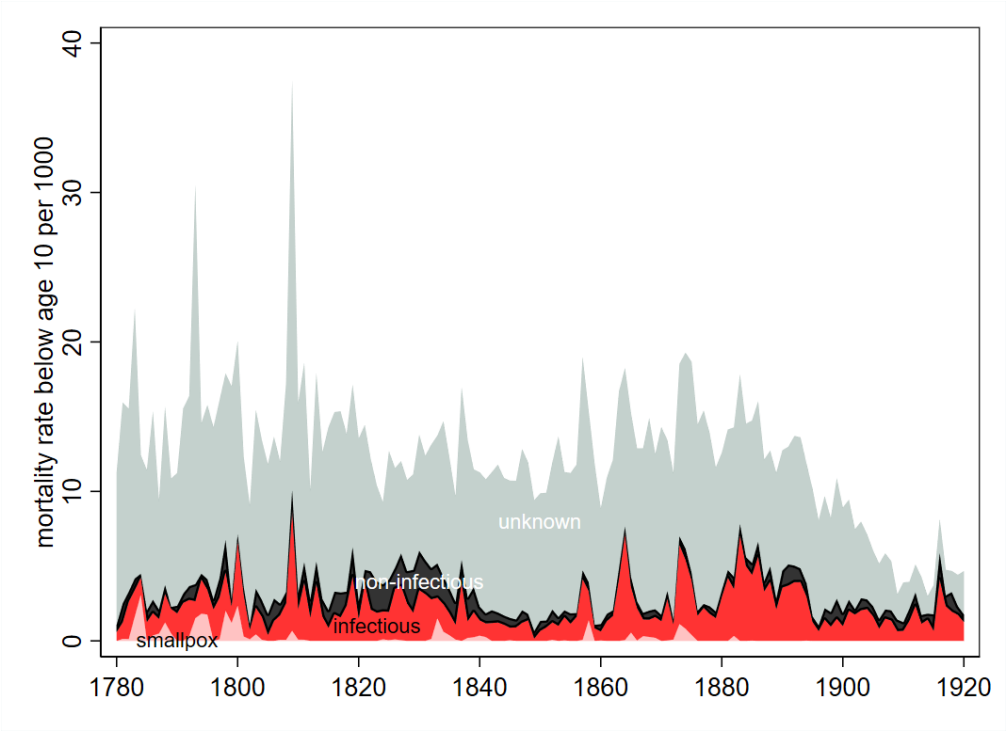


Figure 1 – Mortality rate below age 10 by cause in the area under analysis, 1780–1920

Source: own calculations based on the data from Bengtsson et al. (2021) and CEDAR (2021).

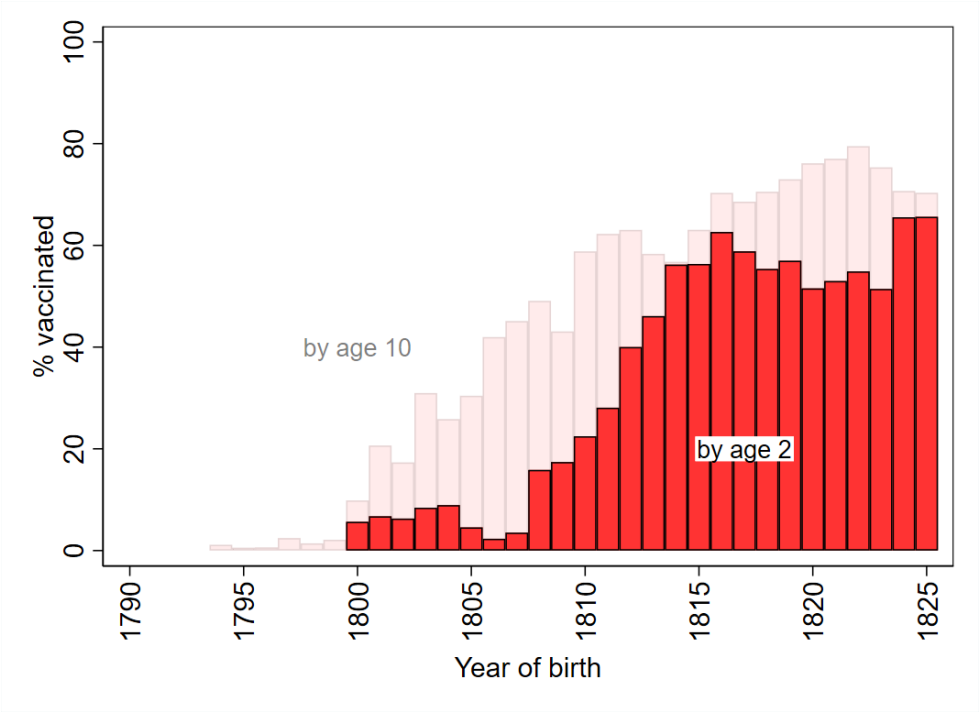


Figure 2 – Share of vaccinated by the age of 2 and later in childhood by year of birth in the area under analysis, 1790–1825

Source: own calculations based on the data from Bengtsson et al. (2021) and CEDAR (2021).

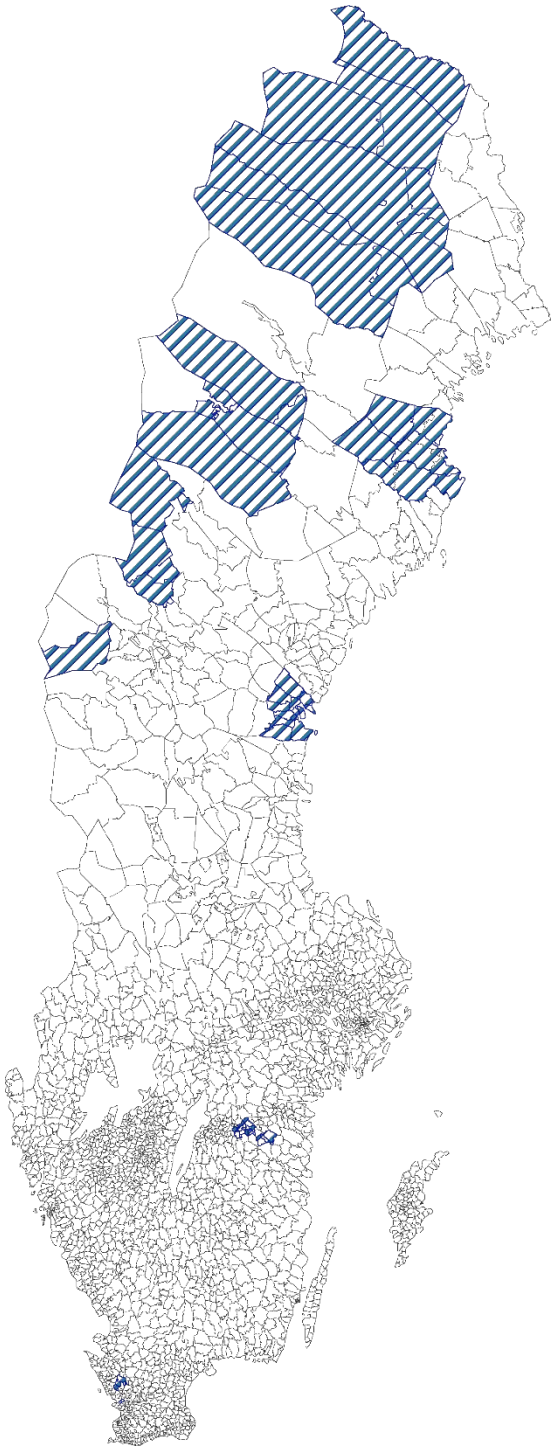
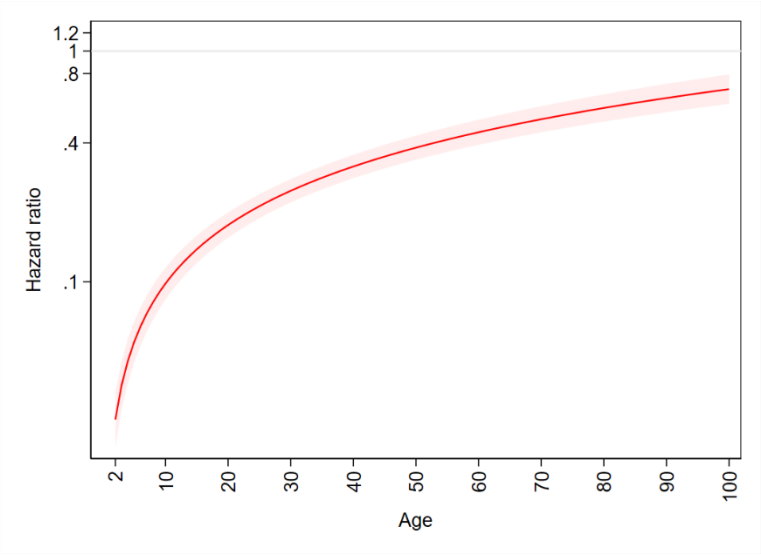
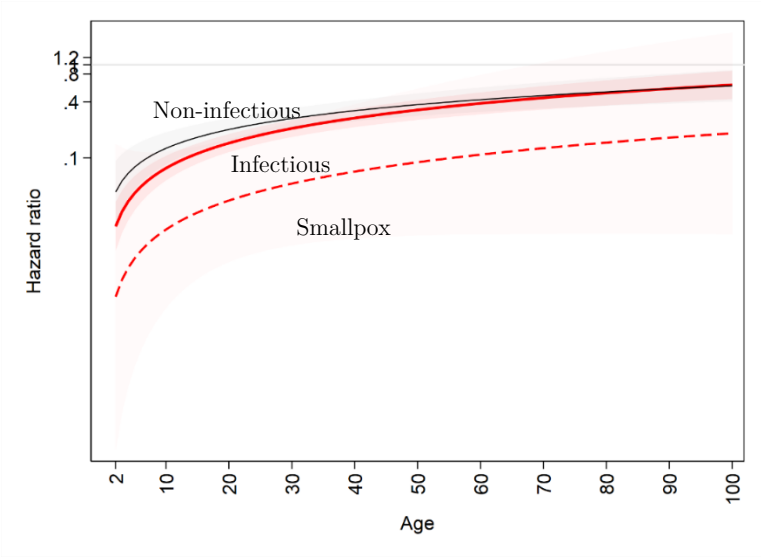


Figure 3 – Parishes under analysis, a snapshot of Sweden in 1820

Sources: Riksarkivet (2016) and the estimation samples from Bengtsson et al. (2021) and CEDAR (2021).



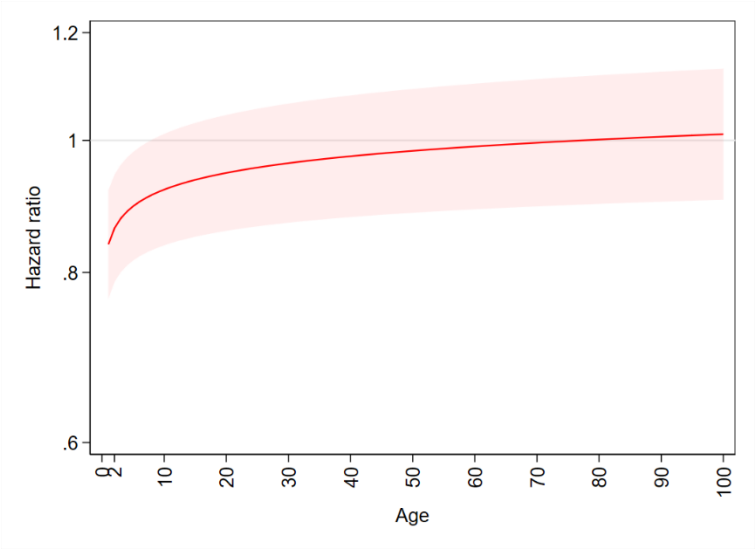
(A) All causes of death



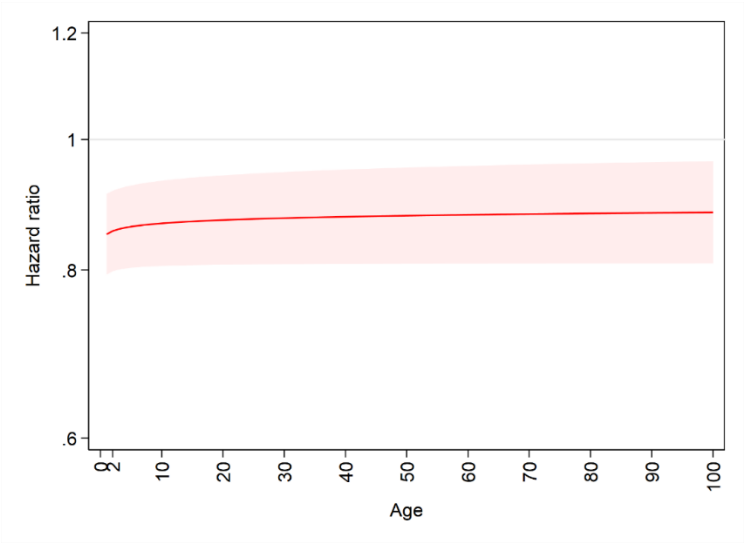
(B) By cause of death

Figure 4 – Age-dependent hazard ratio for the vaccinated before age 2, in total (A) and by cause of death (B), (first generation)

Note: Point estimates and 95% confidence intervals based on the estimates from Eq.1 for the first generation. The full set of estimates is provided in Appendix C Table C.1.



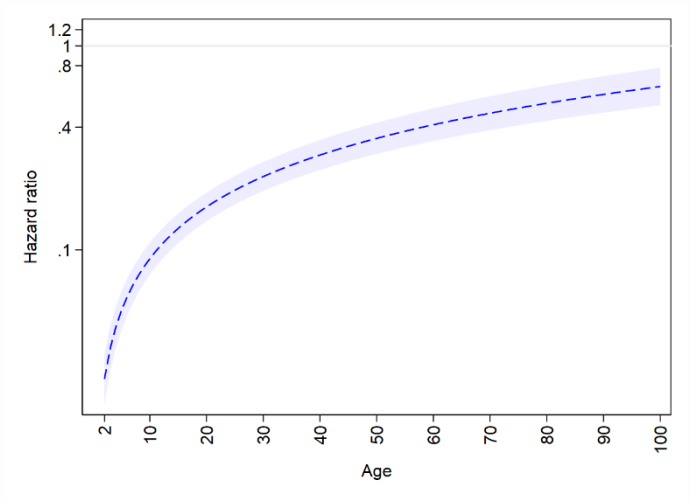
(A) Second generation



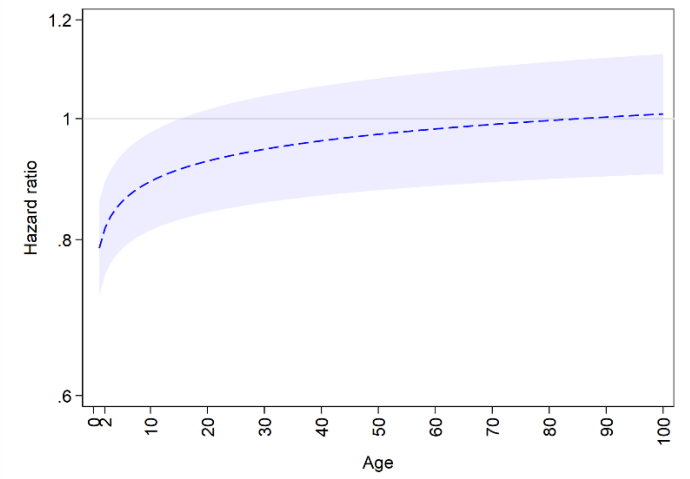
(B) Third generation

Figure 5 – Age-dependent hazard ratio for the vaccinated before age 2 for the second and third generation

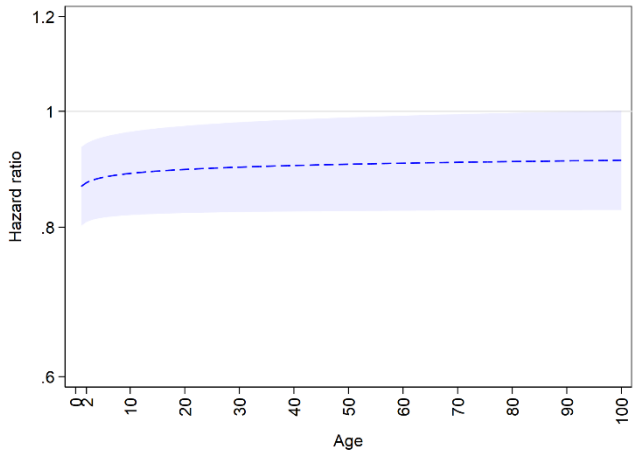
Note: Point estimates and 95% confidence intervals based on the estimates from Eq.1 for the second and third generation. The full set of estimates is provided in Appendix C Table C.2.



(A) First generation



(B) Second generation



(C) Third generation

Figure 6 – Age-dependent hazard ratio for the vaccinated before age 2 based on the IV regressions, (A) first generation, (B) second generation, and (C) third generation.

Note: Point estimates and 95% confidence intervals based on the estimates from Eq.1 for the first generation. Standard errors were bootstrapped. The full set of estimates is provided in Appendix D.

Table 1 – The effects of smallpox vaccination by age 2 on other outcomes in ages 15–50, first generation

	Outcomes		
	Fertility	High SES	Child Vaccinated
	(1)	(2)	(3)
(A) Controlling for observables			
vaccinated by age 2	0.962	1.338***	3.062***
	(0.097)	(0.000)	(0.000)
Individuals	4,378	8,173	11,520
Deaths	8,880	n/a	n/a
Time at risk	81,622	n/a	n/a
Log (pseudo) likelihood	-31,323	-5,057	-13,330
LR (Wald) chi2	500.80	n/a	n/a
(B) 2SRI regressions			
vaccinated by age 2	1.151	1.365***	3.237***
	(0.147)	(0.000)	(0.000)
$\widehat{v_i}$	0.937	0.989	0.989
	(0.016)	(0.015)	(0.016)
Individuals	4,378	8,173	11,520
Deaths	8,880	n/a	n/a
Time at risk	81,622	n/a	n/a
Log (pseudo) likelihood	-24,588	-4,437	-11,919
LR (Wald) chi2	396.89	n/a	n/a

Note: Exponentiated hazard ratios for "Fertility" and logistic regression relative risk ratios for "High SES" and "Child vaccinated" are shown. Standard errors are placed in parentheses. They are bootstrapped in the 2SRI estimations. "Fertility" includes multiple births and only estimated for women. "High SES" is a dummy equal to 1 for HISCLASS less than 5, 0 otherwise. "Child Vaccinated" is a dummy equal to 1 if any of the own children were vaccinated against smallpox, 0 otherwise. Estimates are based on Eq.1 but exclude an age-dependent term, "vaccinated by age 2 x ln(t)".

*** p<0.01, ** p<0.05, * p<0.1

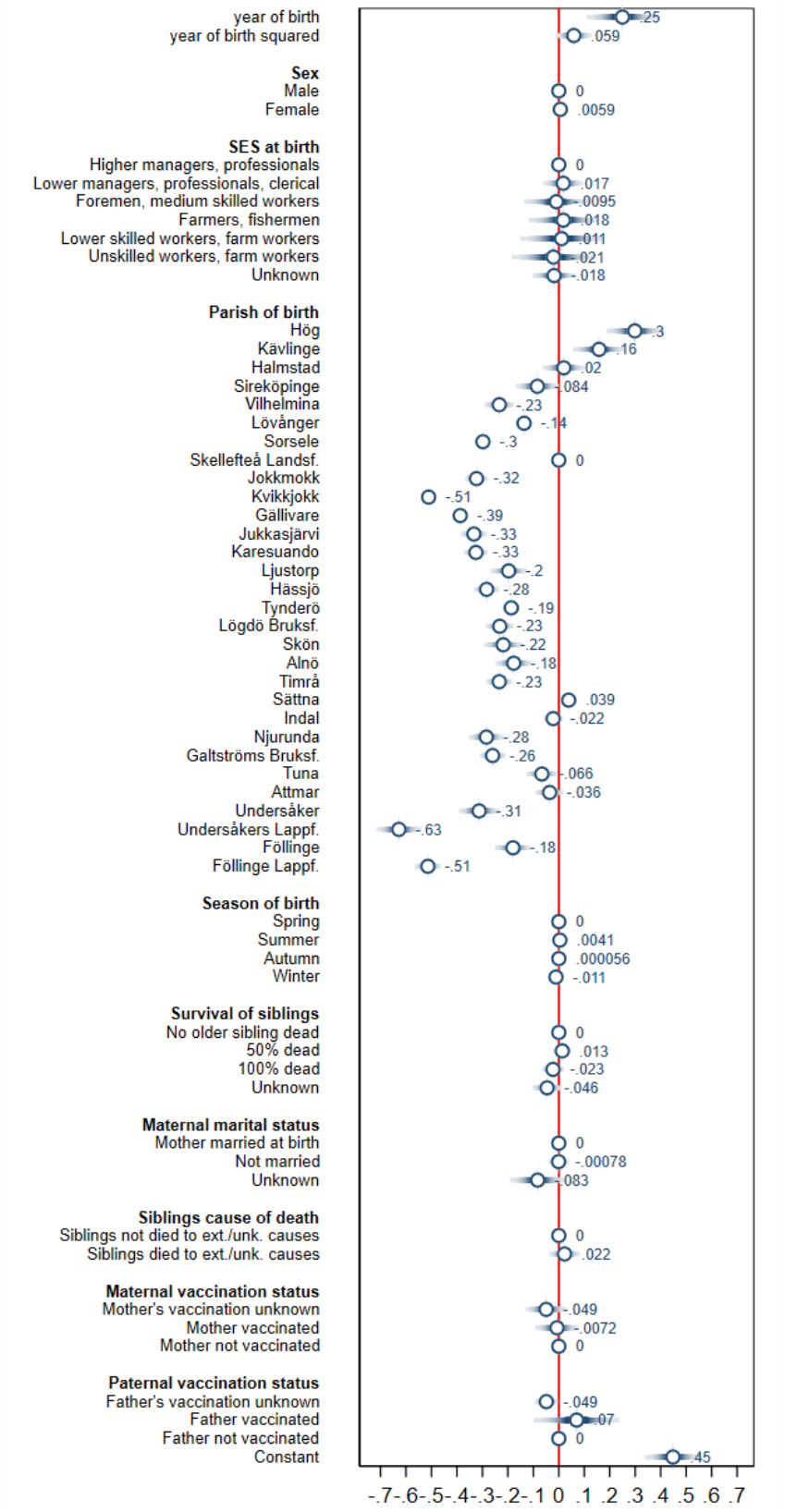
Table 2 – The effects of parental (grandparental) smallpox vaccination by age 2 on SES of second (third) generation in ages 15–50, first generation

	Second generation High SES (1)	Third generation High SES (2)
(A) Controlling for observables		
any parent vaccinated by age 2	1.144***	
	(0.000)	
any grandparent vaccinated by age 2		1.158***
		(0.000)
Individuals	9,134	15,996
Log (pseudo) likelihood	-5,717	-12,889
LR (Wald) chi2	n/a	n/a
(B) 2SRI regressions		
any parent vaccinated by age 2	1.147***	
	(0.000)	
any grandparent vaccinated by age 2		1.164***
		(0.000)
$\widehat{v_i}$ mother's side	0.974	
	(0.016)	
$\widehat{v_i}$ father's side	0.998	
	(0.018)	
$\widehat{v_i}$ grandmother of mother's side		1.000
		(0.016)
$\widehat{v_i}$ grandfather of mother's side		0.986*
		(0.015)
$\widehat{v_i}$ grandmother of father's side		0.999
		(0.017)
$\widehat{v_i}$ grandfather of father's side		0.994
		(0.018)
Individuals	9,134	15,996
Log (pseudo) likelihood	-5,407	-12,968
LR (Wald) chi2	n/a	n/a

Note: Logistic regression relative risk ratios for "High SES" are shown. "High SES" is a dummy equal to 1 for HISCLASS less than 5, 0 otherwise. Standard errors are placed in parentheses. They are bootstrapped in the 2SRI estimations. Estimates are based on Eq.1 but exclude an age-dependent term, "vaccinated by age 2 x ln(t)". In all models, covariates included are parental (grandparental) covariates. In particular, they include maternal and paternal covariates for the second generation, such as both parents' linear and squared terms for the years of birth (recentered), and parishes of birth. In a similar fashion, covariates added to the Eq.1 for the third generation are those for grandmothers and grandfathers. Unknown values for the parental/grandparental year of birth were changed to the year 1820, and for the parental/grandparental parish of birth included into a separate category. Unknown values for the residuals were set to null.

*** p<0.01, ** p<0.05, * p<0.1

Appendix A – Determinants of smallpox vaccination for the first generation



Note: The estimates are from a multivariate regression. Point estimates and 95% confidence intervals. Errors are clustered at the parish of birth. Year of birth was recentered to take the value of 0 for the year of 1801 and divided by its standard deviation.

Appendix B – Description of the instrument

Figure B.1 – Church assistants by parish in the area under analysis in 1780–1830.

Table – Effects of the number of church assistants on the probability of being vaccinated by age 2 from the MLE.

	Ln(Vaccinated by age 2 = 1)
church assistants$_{pt}$	1.091***
	(0.028)
LR chi2 test for "church assistants$_{pt}$"=0	11.19
Individuals	10,226
Log likelihood	-2678.472
LR chi2	8564.13

Note: Odds ratios and standard errors (in parentheses) are shown. The model is estimated according to Eq.2. Individuals were assigned with the number of church assistants available in the parish of their birth before age 2. If they are observed in several years before age 2, which is the most common case, we used the counts of assistants in the last year. There is a small portion of individuals who enter the sample after age 2; those are excluded because the place of vaccination is not known. Some individuals were also omitted because probability was predicted perfectly for their parish of birth.

*** p<0.01, ** p<0.05, * p<0.1

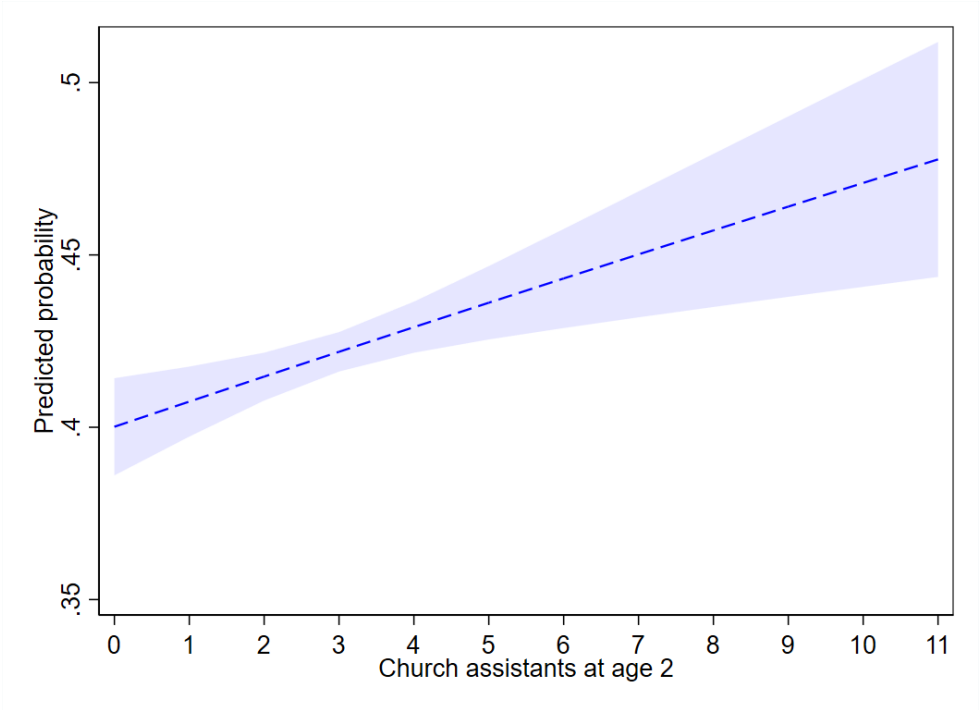


Figure B.2 – Marginal effects of church assistants observed in the parish of birth before age 2 on the individual's response of being vaccinated by age 2.

Note: Both points estimates and 95% confidence intervals are shown. Results are based on estimations of Eq.2 from Appendix B Table above.

Appendix C – Controlling-for-observables estimates of constant and age-dependent smallpox vaccination for three generations

Table C.1 – Age-dependent Cox proportional hazards-model estimates of the effect of smallpox vaccination by age 2 across the life cycle, first generation

	All causes		By cause	
	(1)	(2)	(3)	(4)
vaccinated by age 2	0.235***	0.014***		
	(0.012)	(0.002)		
vaccinated by age 2 x ln(t)		2.323***		
		(0.101)		
vaccinated by age 2 x smallpox			0.022***	0.002***
			(0.016)	(0.004)
vaccinated by age 2 x ln(t) x smallpox				2.814
				(2.002)
vaccinated by age 2 x infectious/respiratory			0.154***	0.010***
			(0.015)	(0.004)
vaccinated by age 2 x ln(t) x infectious/respiratory				2.449***
				(0.267)
vaccinated by age 2 x non-infectious			0.242***	0.027***
			(0.028)	(0.013)
vaccinated by age 2 x ln(t) x non-infectious				1.958***
				(0.259)
vaccinated by age 2 x external			0.138***	0.019***
			(0.030)	(0.017)
vaccinated by age 2 x ln(t) x external				1.939**
				(0.549)
vaccinated by age 2 x unknown			0.272***	0.017***
			(0.016)	(0.003)
vaccinated by age 2 x ln(t) x unknown				2.261***
				(0.117)
Individuals	11,734	11,734	58,670	58,670
Deaths	3,623	3,623	3,623	3,623
Time at risk	215,124	215,124	1,075,620	1,075,620
Log likelihood	-27,119	-26,866	-27,087	-26,857
LR chi2	1127.23	1634.52	1192.47	1651.53

Note: Exponentiated hazard ratios and standard errors (in parentheses) are shown. Estimates in odd columns exclude an age-dependent term, vaccinated by age 2 x ln(t), form Eq.1. Estimates in even columns are based on Eq.1. For the cause-specific hazard, the deaths were stacked five times (i.e. as many as the groups of causes were to be estimated) and then estimated with Eq.1 stratified by cause.

*** p<0.01, ** p<0.05, * p<0.1

Table C.2 – Age-dependent Cox proportional hazards-model estimates of the effect of parental and grandparental smallpox vaccination by age 2 across the life cycle, second and third generation

	Second generation		Third generation	
	(1)	(2)	(3)	(4)
any parent vaccinated by age 2	0.865***	0.838***		
	(0.039)	(0.039)		
any parent vaccinated by age 2 x ln(t)		1.042***		
		(0.009)		
any grandparent vaccinated by age 2			0.853***	0.850***
			(0.029)	(0.029)
any grandparent vaccinated by age 2 x ln(t)				1.008
				(0.006)
Individuals	14,768	14,768	30,531	30,531
Deaths	6,384	6,384	10,389	10,389
Time at risk	294,043	294,043	531,490	531,490
Log likelihood	-54,078	-54,067	-97,610	-97,610
LR chi2	303.77	326.98	501.98	503.48

Note: Exponentiated hazard ratios and standard errors (in parentheses) are shown. Estimates in odd columns exclude an age-dependent term, vaccinated by age 2 x ln(t), from Eq.1. Estimates in even columns are based on Eq.1. In all models, covariates included are parental (grandparental) covariates. In particular, they include maternal and paternal covariates for the second generation, such as both parents' linear and squared terms for the years of birth (recentered), and parishes of birth. In a similar fashion, covariates added to the Eq.1 for the third generation are those for grandmothers and grandfathers. Unknown values for the parental/grandparental year of birth were changed to the year 1820, and for the parental/grandparental parish of birth included into a separate category.

*** p<0.01, ** p<0.05, * p<0.1

Appendix D – IV estimates of constant and age-dependent smallpox vaccination for three generations

Table – 2SRI (IV) estimates of the effect of smallpox vaccination by age 2 across the life cycle based on age-dependent Cox proportional-hazards model, (1) first generation, (2) second generation, and (3) third generation.

	All causes		All causes		All causes	
	(1)	(2)	(3)	(4)	(5)	(6)
vaccinated by age 2	0.208***	0.013***				
	(0.019)	(0.002)				
vaccinated by age 2 x ln(t)		2.324***				
		(0.107)				
any parent vaccinated by age 2			0.811***	0.787***		
			(0.037)	(0.034)		
any parent vaccinated by age 2 x ln(t)				1.055***		
				(0.009)		
any grandparent vaccinated by age 2					0.868***	0.865***
					(0.037)	(0.033)
any grandparent vaccinated by age 2 x ln(t)						1.007
						(0.003)
$\widehat{\nu_i}$	0.997	1.005				
	(0.013)	(0.010)				
$\widehat{\nu_i}$ mother's side			1.000	1.000		
			(0.009)	(0.009)		
$\widehat{\nu_i}$ father's side			1.000	1.001		
			(0.009)	(0.009)		
$\widehat{\nu_i}$ grandmother of mother's side					1.000	1.000
					(0.009)	(0.009)
$\widehat{\nu_i}$ grandfather of mother's side					0.981*	0.981*
					(0.010)	(0.010)
$\widehat{\nu_i}$ grandmother of father's side					1.019*	1.019*
					(0.012)	(0.011)
$\widehat{\nu_i}$ grandfather of father's side					0.996	0.996
					(0.011)	(0.011)
Individuals	10,226	10,226	13,554	13,554	28,481	28,481
Deaths	3,076	3,076	5,795	5,795	9,566	9,566
Time at risk	185,648	185,648	266,862	266,862	497,697	497,697
Log likelihood	-22,548	-22,322	-48,657	-48,639	-89,335	-89,334
LR chi2	774.87	2082.28	653.99	322.08	407.27	409.75

Note: Exponentiated hazard ratios and standard errors (in parentheses) are shown. Estimates in odd columns exclude an age-dependent term, vaccinated by age 2 x ln(t), form Eq.3. Estimates in even columns are based on Eq.3. Standard errors were bootstrapped. There is a small portion of individuals who enter the sample after age 2; those were excluded because the place of vaccination is not known. Some individuals were also omitted because probability was predicted perfectly for their parish of birth.

*** p<0.01, ** p<0.05, * p<0.1

Appendix E – Causal mediation effects for subsequent generations

Table – Natural direct and indirect effects of parental (grandparental) smallpox vaccination status on survival of second (third) generation

	Mediators		
	Year of Birth	High Parental SES	Own Vaccination Status
	(1)	(2)	(3)
Panel A – Second generation			
any parent vaccinated by age 2			
"Natural Direct Effect"	0.561***	0.354***	0.370***
	(0.051)	(0.074)	(0.073)
"Natural Indirect Effect"	1.000	1.002	0.951
	(1.441)	(1.584)	(0.338)
Individuals	14,768	14,768	14,768
Deaths	6,385	6,385	6,385
Time at risk	294,043	294,043	294,043
Log (pseudo) likelihood	-6.528e+10	-5.630e+10	-1.135e+09
LR (Wald) chi2	4.85	13.07	12.86
Panel B – Third generation			
any grandparent vaccinated by age 2			
"Natural Direct Effect"	0.339***	0.337***	0.338***
	(0.109)	(0.097)	(0.098)
"Natural Indirect Effect"	1.000	1.000	1.000
	(0.239)	(0.239)	(0.239)
Individuals	30,531	30,531	30,531
Deaths	10,389	10,389	10,389
Time at risk	531,490	531,490	531,490
Log (pseudo) likelihood	-4.215e+11	-1.965e+11	-2.084e+11
LR (Wald) chi2	12.09	14.23	14.10

Note: Exponentiated hazard ratios and bootstrapped standard errors (in parentheses) are shown. Estimates are based on the weighting approach by Lange, Vansteelandt, and Bekaert (2012), where the treatment is a constant term for any parent (any grandparent) "vaccinated by age 2" for the second (third) generation, mediators are the individual's year of birth (a binary term split at the median and equal to 1 for younger cohorts, 0 otherwise), parental SES (a binary term equal to 1 for HISCLASS less than 5, 0 otherwise) and own vaccination status (binary equal to 1 if vaccinated against smallpox, 0 otherwise) included into the estimations separately, and covariates are the same as in Eq.1 for the second (third) generation.

*** p<0.01, ** p<0.05, * p<0.1

Appendix F – Acquired immunity for the first generation

Table F.1 – Age-dependent Cox proportional hazards-model estimates of the effect of smallpox vaccination and smallpox infection by age 2 across the life cycle, first generation

	All causes	
	(1)	(2)
vaccinated by age 2	0.202***	0.010***
	(0.012)	(0.002)
vaccinated by age 2 x ln(t)		2.474***
		(0.121)
infected by age 2	0.356***	0.003***
	(0.058)	(0.004)
infected by age 2 x ln(t)		3.787***
		(1.150)
Individuals	10,044	10,044
Deaths	3,165	3,165
Time at risk	176,285	176,285
Log likelihood	-23,318	-23,072
LR chi2	1406.96	1897.96

Note: Exponentiated hazard ratios and standard errors (in parentheses) are shown. Estimates in odd columns exclude an age-dependent term, vaccinated by age 2 x ln(t), form Eq.1. Estimates in even columns are based on Eq.1. Individuals who were infected after age 2 are excluded.

*** p<0.01, ** p<0.05, * p<0.1

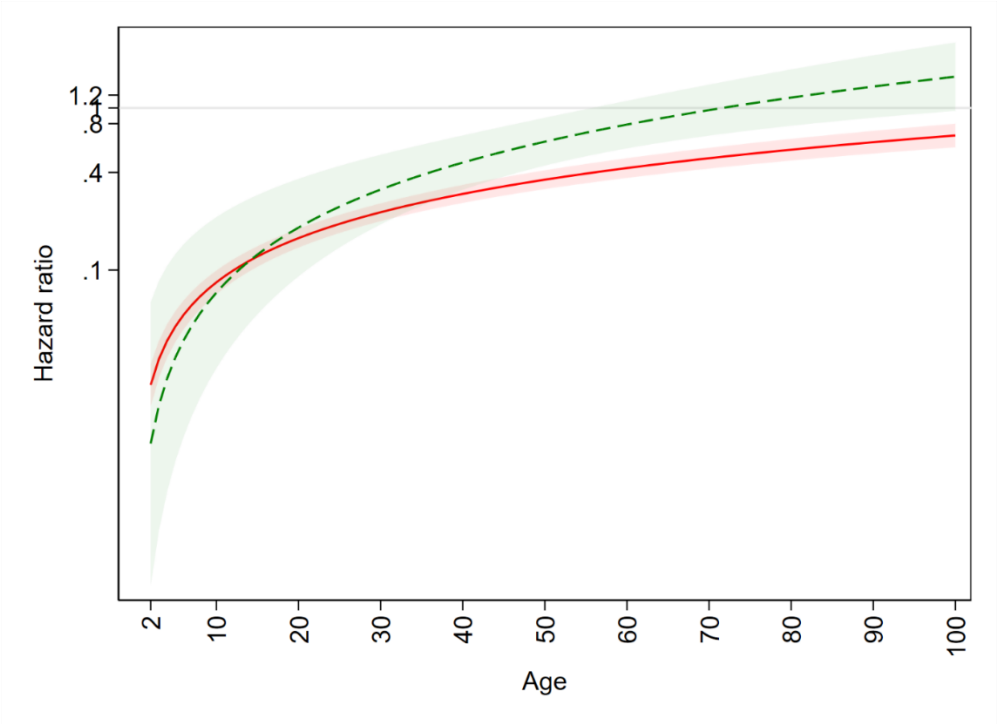


Figure – Age-dependent hazard ratios for the vaccinated and the infected before age 2, first generation

Note: Point estimates and 95% confidence intervals based on the estimates from Eq.1 for the first generation.

Appendix G – Sensitivity analysis with E-value

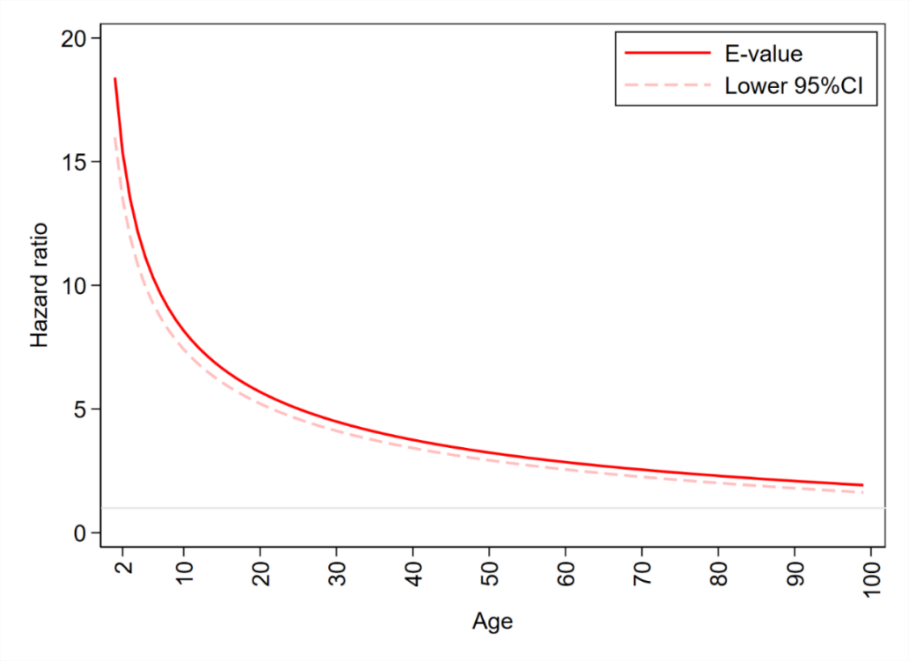


Figure G.1 – E-value for the effect of smallpox vaccination by age 2 across the life cycle, first generation

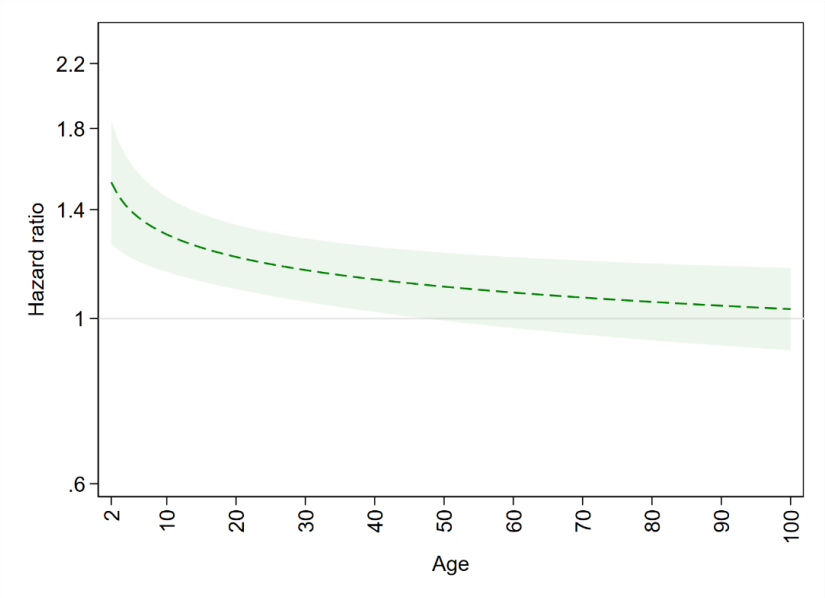
Note: E-value and lower 95%-CI are presented.

Table G.1 – Age-dependent Cox proportional hazards-model estimates of the effect of smallpox vaccination and smallpox infection by age 2 across the life cycle, first generation

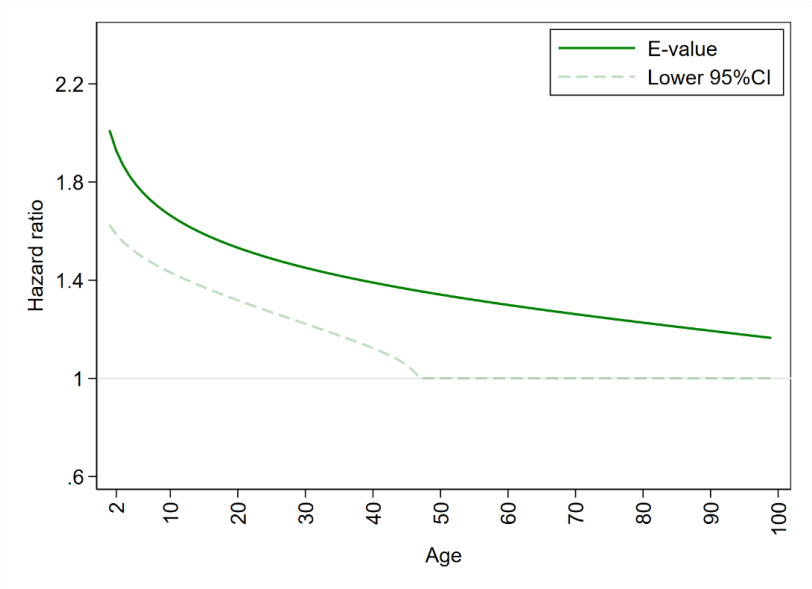
	All causes	
	(1)	(2)
born out of wedlock	1.178***	1.634***
	(0.058)	(0.190)
born out of wedlock x ln(t)		0.905***
		(0.029)
Individuals	11,734	11,734
Deaths	3,623	3,623
Time at risk	215,124	215,124
Log likelihood	-27,458	-27,453
LR chi2	451.7	461.7

Note: Exponentiated hazard ratios and standard errors (in parentheses) are shown. Estimates in odd columns exclude an age-dependent term, born out of wedlock x ln(t), form Eq.1. Estimates in even columns are based on Eq.1. Individuals who were infected with smallpox after age 2 are excluded.

*** p<0.01, ** p<0.05, * p<0.1



(A) Hazard ratio



(B) E-value and lower 95%-CI

Figure G.2 – Age-dependent hazard ratio (Panel A) and its e-value (Panel B) for the born out of wedlock, first generation

Note: Point estimates and 95% confidence intervals based on the estimates from Eq.1 for the first generation.

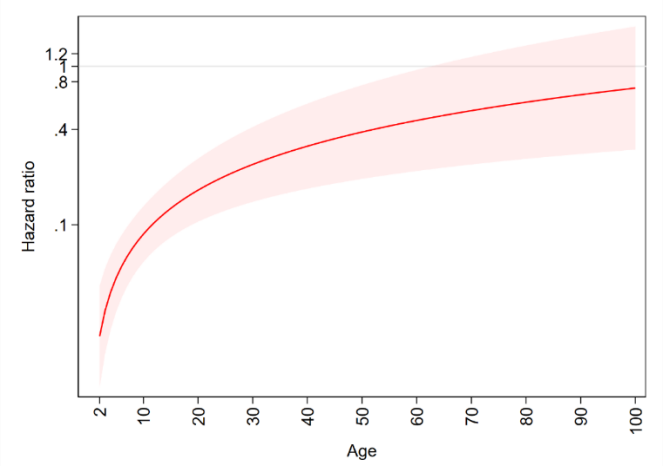
Appendix H – Siblings/First Cousins/Second Cousins Fixed Effects

Table – Age-dependent Cox proportional hazards-model estimates of the effect of smallpox vaccination by age 2 across the life cycle, (1) first generation, (2) second generation, and (3) third generation.

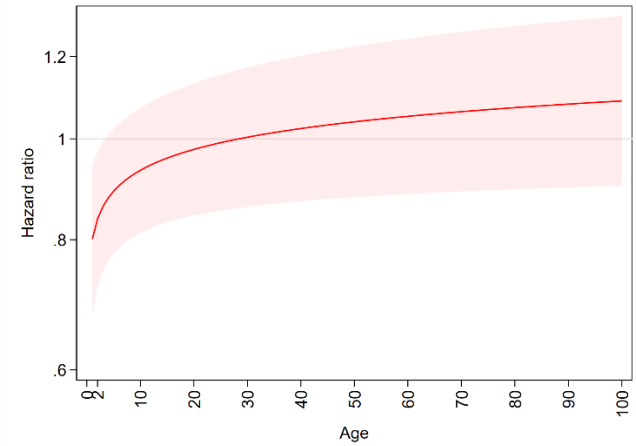
	First generation (Siblings' baseline hazards)		Second generation (First cousins' baseline hazards)		Third generation (Second cousins' baseline hazards)	
	(1)	(2)	(3)	(4)	(5)	(6)
vaccinated by age 2	0.073***	0.013***				
	(0.014)	(0.002)				
vaccinated by age 2 x ln(t)		2.324***				
		(0.107)				
any parent vaccinated by age 2			0.904	0.800***		
			(0.063)	(0.067)		
any parent vaccinated by age 2 x ln(t)				1.069***		
				(0.026)		
any grandparent vaccinated by age 2					0.824***	0.821***
					(0.0.9)	(0.039)
any grandparent vaccinated by age 2 x ln(t)						0.984
						(0.016)
Individuals	11,734	11,734	14,768	14,768	30,531	30,531
Deaths	3,623	3,623	6,384	6,384	10,389	10,389
Time at risk	215,124	215,124	294,043	294,043	531,490	531,490
Log likelihood	-1,585	-1,572	-12,620	-12,616	-24,630	-24,630
LR chi2	317.84	345.09	2.16	9.86	16.49	17.38

Note: Exponentiated hazard ratios and standard errors (in parentheses) are shown. Fixed effects models were estimated by modeling sibling (first cousin/ second cousin)-specific baseline hazards. Estimates in odd columns exclude an age-dependent term, vaccinated by age 2 x ln(t), from Eq.1. Except for the vaccination terms, no other covariates were included.

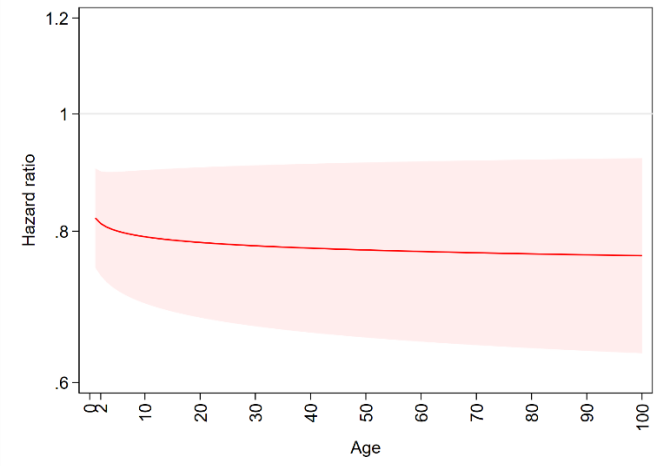
*** p<0.01, ** p<0.05, * p<0.1



(A) First generation



(B) Second generation



(C) Third generation

Figure – Age-dependent hazard ratio for the first (Panel A), second (Panel B) and third generation (Panel C) for the vaccinated and the infected before age 2

Note: Point estimates and 95% confidence intervals based on the estimates from Eq.1 where fixed effects models were estimated by specifying a sibling (first cousin/ second cousin)-specific baseline hazard and no more other covariates were included.

Lund Papers in Economic History
ISRN LUSADG-SAEH-P--21/232SE+58

Orders of printed single back issues (no. 1-65)
Department of Economic History, Lund University
Postal address: P.O. Box 7083, S-220 07 Lund, Sweden
Telephone: +46 46 2227475
Telefax: +46 46 131585

Full-text electronic issues (no. 58, 60, 61, 66--)
www.ekh.lu.se

Lund Papers in Economic History are published by the Department of Economic History, Lund University, Sweden. This series replaces the former series under the title *Meddelande från ekonomisk-historiska institutionen, Lunds universitet*. The change of name reflects the orientation of the series towards an international readership. The series is multilingual, but the majority of the working papers appear in English.

Lund Papers in Economic History are published as occasion arises, not at fixed intervals. Printed issues are distributed to libraries. From 1999 and onwards, full-text electronic issues are also available on *www.ekh.lu.se.* Those who would be interested in receiving information by email on new issues of **Lund Papers in Economic History** are requested to send an email message to *Lund.Papers@ekh.lu.se.*

LUND
UNIVERSITY