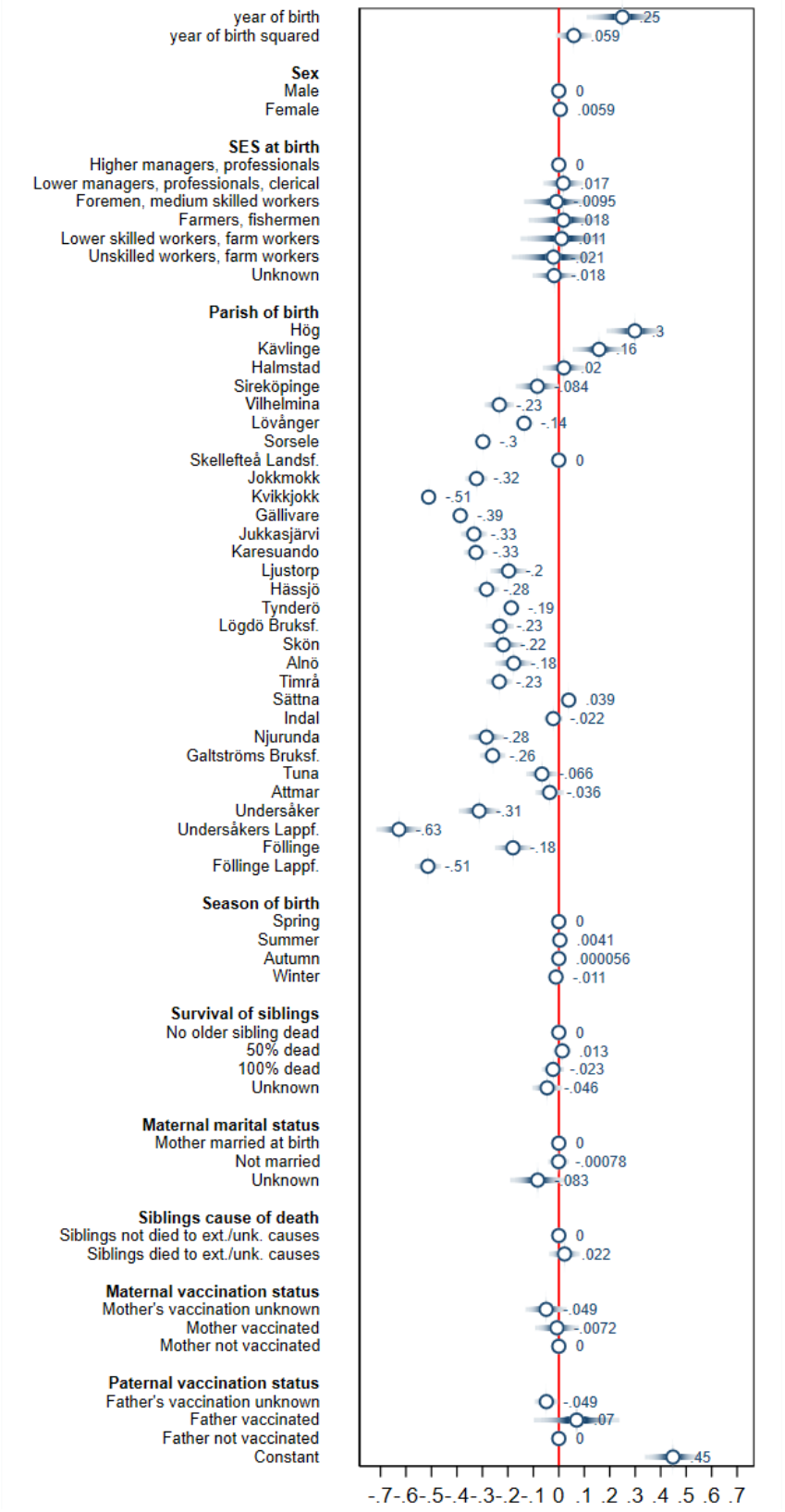
Appendix A – Determinants of smallpox vaccination for the first generation



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

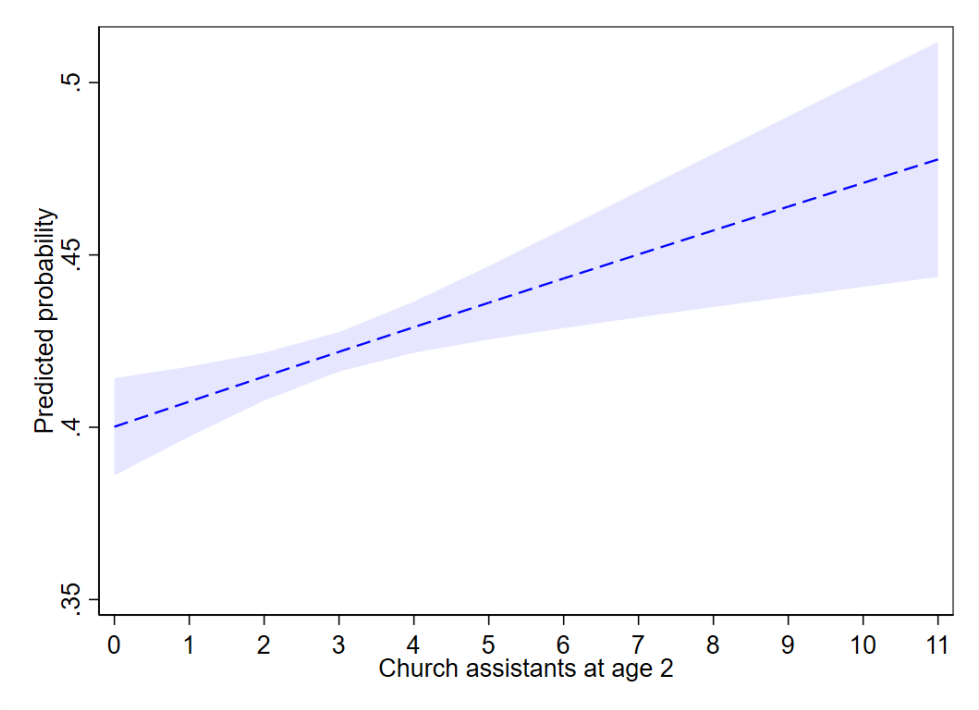


Figure B.2 – Marginal effects of church assistants observed in the parish of birth before age 2 on the individual's response of being vaccinated by age 2.

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

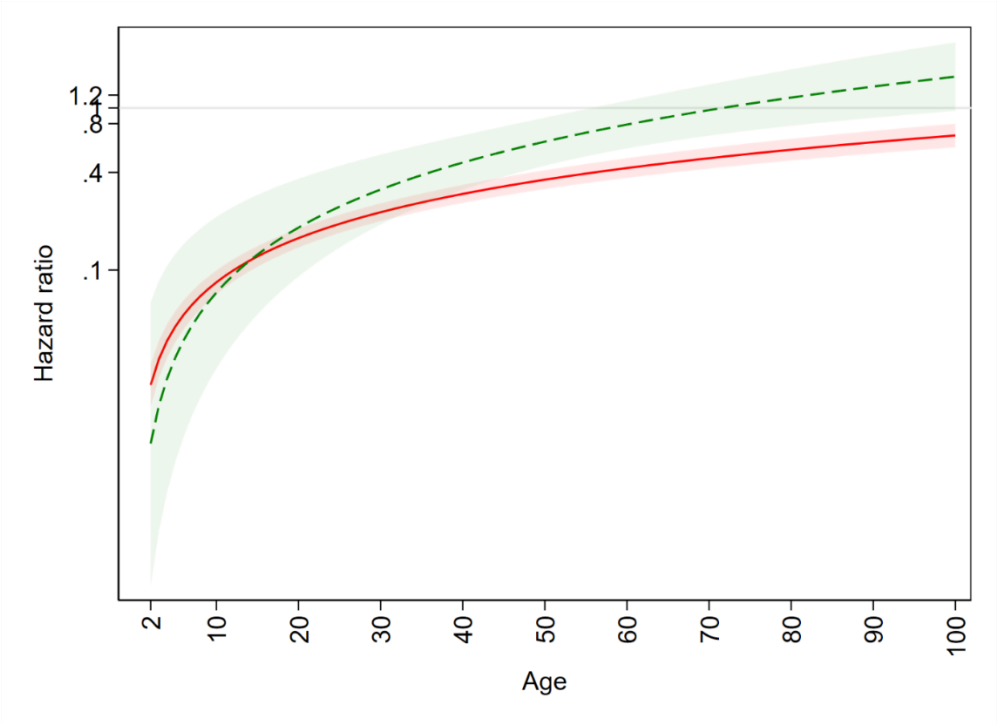


Figure – Age-dependent hazard ratios for the vaccinated and the infected before age 2, first generation

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

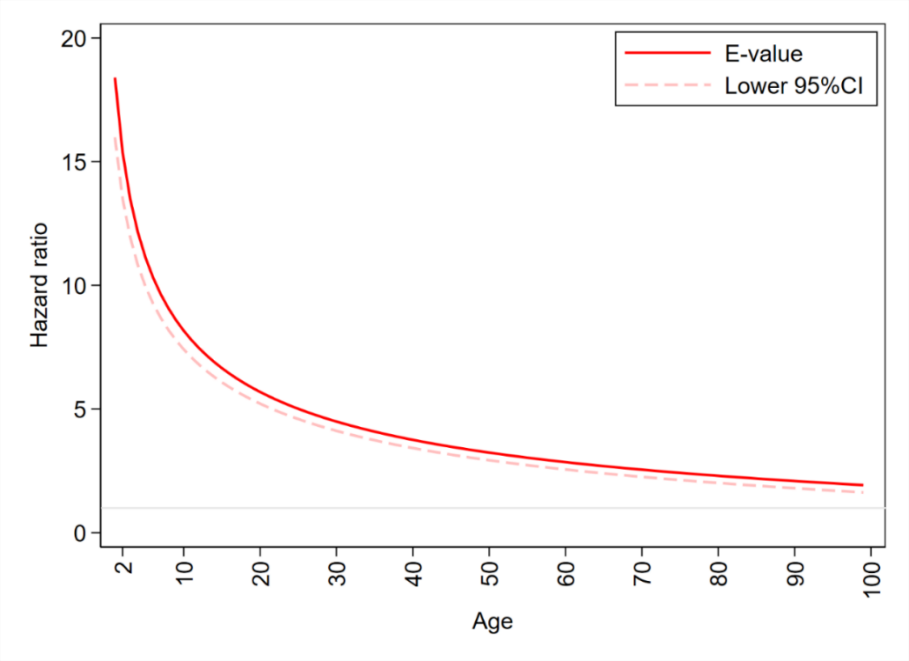


Figure G.1 – E-value for the effect of smallpox vaccination by age 2 across the life cycle, first generation

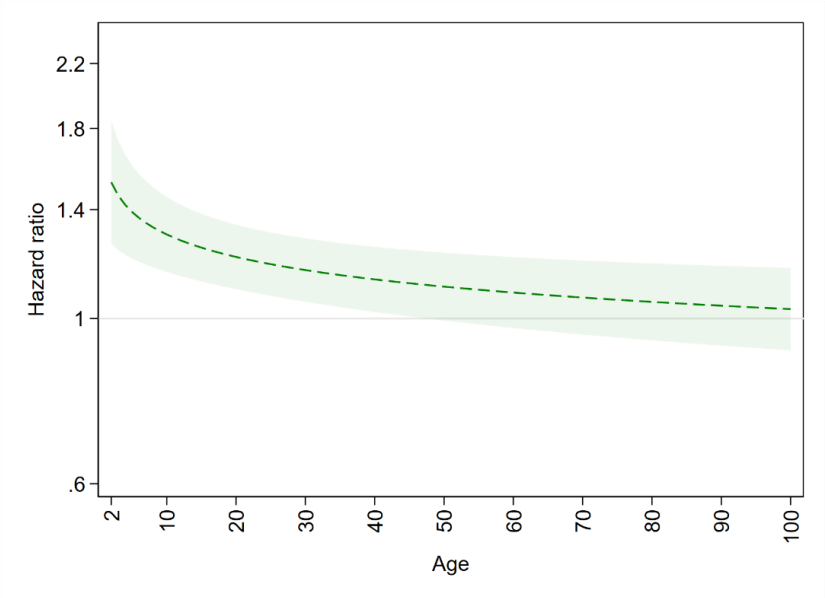
Note: E-value and lower 95%-CI are presented.

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

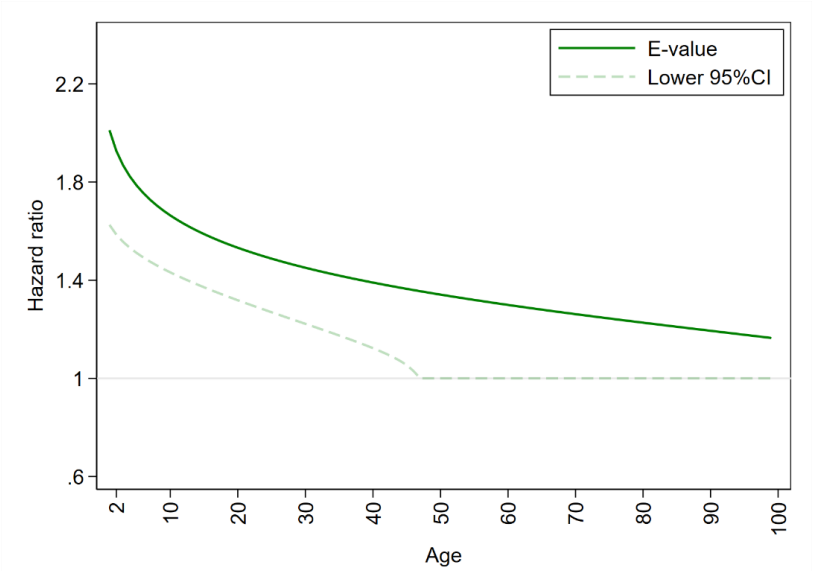
	All causes	
	(1)	(2)
born out of wedlock	1.178***	1.634***
	(0.058)	(0.190)
born out of wedlock x ln(t)		0.905***
		(0.029)
Individuals	11,734	11,734
Deaths	3,623	3,623
Time at risk	215,124	215,124
Log likelihood	-27,458	-27,453
LR chi2	451.7	461.7

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.

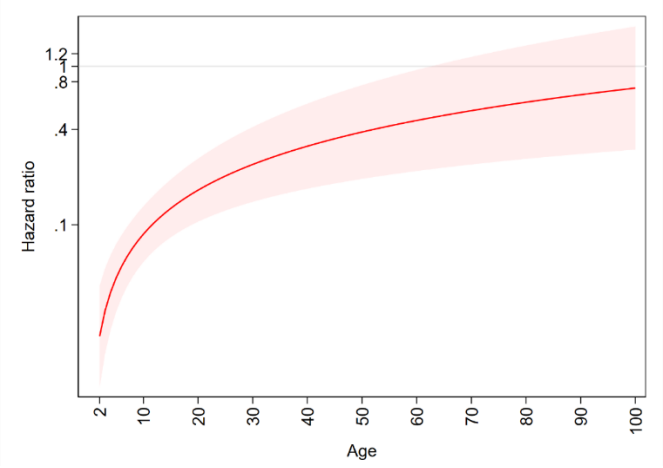
Appendix H – Siblings/First Cousins/Second Cousins Fixed Effects

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.

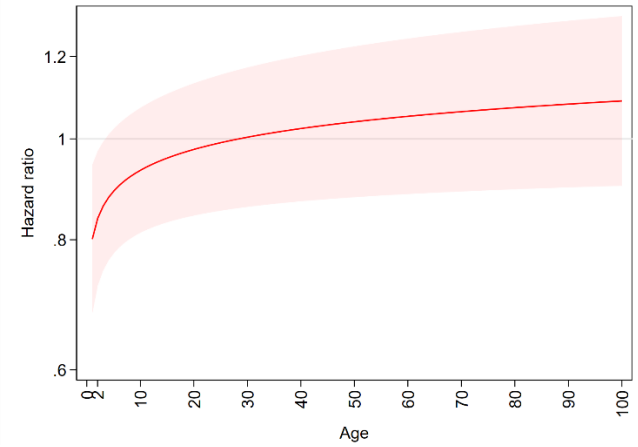
	First generation (Siblings' baseline hazards)		Second generation (First cousins' baseline hazards)		Third generation (Second cousins' baseline hazards)	
	(1)	(2)	(3)	(4)	(5)	(6)
vaccinated by age 2	0.073***	0.013***				
	(0.014)	(0.002)				
vaccinated by age 2 x ln(t)		2.324***				
		(0.107)				
any 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.

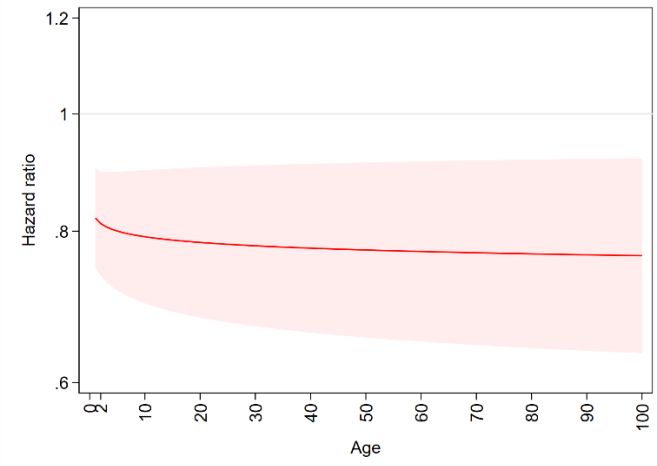
*** p<0.01, ** p<0.05, * p<0.1



(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.