Birth order, maternal immunisations, and infant infections

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IDI disclaimer

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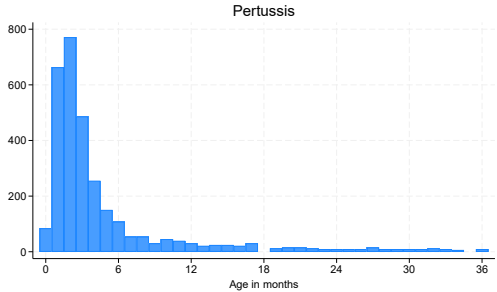
Introduction

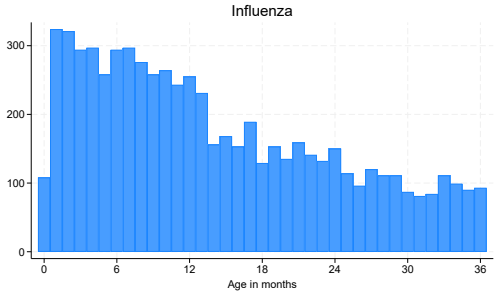
- pregnancy and infancy are periods of increased vulnerability to infections
- maternal immunisations: protect pregnant women and their infants, but uptake remains low
  - US survey: 47.2 % received influenza, 55.4 % Tdap during pregnancy (Razzaghi et al., 2023)
  - NZ administrative data 2018: 30.8 % received influenza, 43.6 % Tdap (Howe et al., 2020)
- growing evidence that birth order affects early childhood health and parental behaviour
  - lower uptake of childhood immunisations (Pruckner et al., 2021)
  - higher rates of hospitalisations and drug prescriptions for contagious diseases in early life (Pruckner et al., 2021; Daysal et al., 2021)
- this paper: studies the relationship between
  - birth order and maternal immunisation against pertussis and influenza
  - birth order and childhood hospitalisation due to these diseases

Why should birth order matter?

- parental investment and behavior
  - time and financial constraints, parenting style (Price, 2008)
  - mothers are less likely to attend pre-natal care and breastfeed later-born children (Buckles and Kolka, 2014; Brenøe and Molitor, 2018; Lehmann et al., 2018)
  - later-born children are less likely to participate in preventive medical health checks and have lower childhood immunisation uptake (Pruckner et al., 2021; Lin et al., 2022)
- biological reasons
  - nutrition availability increases with each pregnancy
  - later-born children are healthier at birth (Brenøe and Molitor, 2018; Pruckner et al., 2021; Björkegren and Svaleryd, 2023)
- family environment: influence of (older) siblings
  - older children can 'bring home' common viruses or bacteria
  - younger siblings have higher rates respiratory/infectious conditions in early life (Pruckner et al., 2021; Daysal et al., 2021)
- endogeneity and selection explanations

Pertussis and influenza hospitalisations in NZ





- repeated **pertussis** (= whooping cough) outbreaks in New Zealand
  - young infants face a higher risk of hospitalisation and death (Kandeil et al., 2020)
- annual **influenza** seasons
  - approximately 1 in 5 unvaccinated children and 1 in 10 unvaccinated adults infected by seasonal influenza annually (Somes et al., 2018)
- potential long-term effects: brain development (Al-Haddad et al., 2019), socio-economic outcomes (Almond, 2006)

Maternal immunisation

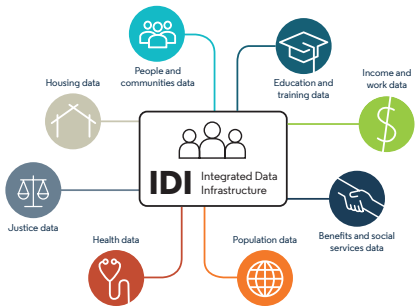
- 2 benefits of vaccination during pregnancy
  - protecting women during pregnancy and the fetus from congenital infections and other harmful effects
  - transfer of maternal antibodies to infants via placental transfer and/or breastfeeding
- vaccine effectiveness in infants of immunised mothers
  - pertussis: 69-91 % for pertussis prevention; 91-94 % for hospitalisation, 95 % for death (Vygen-Bonnet et al., 2020)
  - influenza: 48 % and 72 % reduced risk of infants having laboratory-confirmed influenza infection and associated hospitalization (Nunes and Madhi, 2018)
- maternal immunisations recommended and funded in many countries, including NZ
  - pertussis: for all pregnant women since 2013
    - originally funded when given from 28 to 38 weeks' gestation
    - since 2019 funded when given any time in second or third trimester
  - influenza: since 2010
    - recommended from 1 April, before usual May to September influenza virus activity
    - any trimester
  - covid: recommended since June 2021

Childhood immunisation

- National Immunisation Schedule includes three acellular pertussis-containing vaccines in the first year of life
  - 6-in-1 vaccine at 6 weeks, 3 months, 5 months: diphtheria, tetanus, acellular pertussis, polio, hepatitis B, Haemophilus influenzae type b
  - booster doses at ages 4 and 11 years
- additional first-year vaccinations: rotavirus, PCV (Pneumococcal vaccine), MMR (measles), Meningococcal B (since 2013)
- influenza: recommended for everyone over 6 months of age; publicly funded for children only if they have certain chronic conditions
  - only 4.4 % of children under five received the vaccine in 2018 (Marsh et al., 2024)
  - free influenza vaccines for children in 2022, abandoned in 2024
- maternal immunisation to fill the gap until infants can build up their own immunity

Integrated Data Infrastructure (IDI)

- population-wide research database managed by StatsNZ
- linked micro-data from government agencies, NGOs, surveys
  - births from Department of Internal Affairs (DIA)
  - vaccine type and date from Aotearoa Immunisation Register (AIR) *(replaced the National Immunisation Register)*
  - hospital discharge records from Ministry of Health (MoH) with diagnostic information
  - National Maternity Collection: visits to lead maternity carer



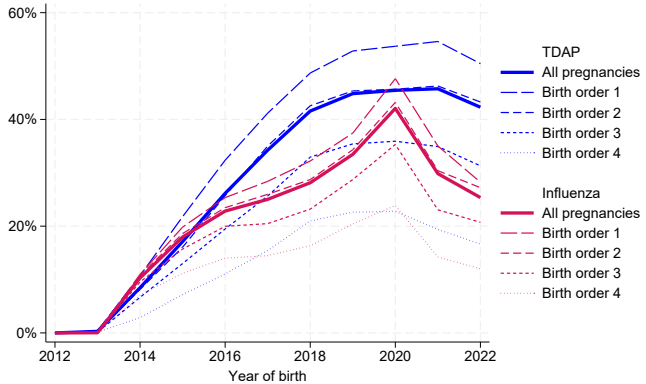
Empirical strategy

$$Y_{im} = \alpha + \sum_j \beta_j I(BO_{im} = j) + \gamma X_i + \delta_m + \epsilon_{im},$$

Y_{im}	outcome of pregnancy/child i of mother m
$BO_{im} = j$	birth order indicators (j = 2, 3, 4+)
X_i	sex, year-by-month of birth
δ_m	mother fixed effects

- exploit within-family variation in birth order to account for time-constant unobserved factors at the family level (e. g., genetic endowment, SES)
- main sample: children born between 2015-2023 for maternal immunisations
  - mother with at least 2 births
  - excluding mothers with multiple births $\rightarrow$ birth order = order of pregnancies
- alternative specification with linear birth order effect
- assumption: family size is exogenous to children's health endowment

Immunisation trends



- similar to Howe et al. (2020)
  - using supplementary data on payments made to GPs for vaccination and pharmaceutical claims for vaccine dispensing
  - 43.6 % received pertussis and 30.9 % influenza vaccine in 2018

Effects of birth order on immunisations

	(1) Maternal Tdap	(2) Maternal Influenza	(3) All infant immunisations
Birth order 2	-0.069^{***}	-0.013^{***}	-0.016^{***}
	(0.004)	(0.004)	(0.001)
Birth order 3	-0.112^{***}	-0.043^{***}	-0.031^{***}
	(0.007)	(0.007)	(0.002)
Birth order 4	-0.163^{***}	-0.099^{***}	-0.057^{***}
	(0.012)	(0.011)	(0.004)
N	209,049	209,049	503,118
Mean	0.426	0.322	0.913

Notes: Births between 2015 and 2023 in columns 1-2, and births between 2008 and 2023 in column 3. Regressions include mother fixed effects, year by month of birth fixed effects, and a female indicator. The mean of the dependent variable is displayed at the bottom of the table. Standard errors in parentheses are clustered at the mother level. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Why do maternal immunisations decrease with birth order?

- mothers may believe immunisation during an earlier pregnancy provides sufficient protection
  - test: use a sample of mothers who received maternal immunisation during their first pregnancy and had at least two subsequent pregnancies
  - would expect a higher vaccine uptake for the third pregnancy compared to the second
- adverse effects of immunisation at earlier pregnancies?
  - medical literature suggests severe side-effects are rare
  - test: control for hospitalisations during previous pregnancy
- significant birth order effects also number of visits to LMC and ultrasounds during pregnancy
  - less recommendations/opportunities for vaccinations
  - but controlling for number of visits does not affect birth order effects substantially
  - generally lower uptake of services during pregnancy $\rightarrow$ parental behaviour and resources (time constraints)?

Effects of birth order on infant hospitalisations for infectious diseases

	Pertussis		Influenza	
	(1) ≤12 months	(2) ≤3 months	(3) ≤12 months	≤3 months
Birth order 2	39.7**	29.3**	49.9**	46.4***
	(13.1)	(11.4)	(17.8)	(9.3)
Birth order 3	79.0**	72.5**	104.4**	69.5***
	(26.5)	(23.3)	(36.1)	(18.8)
Birth order 4	109.0*	81.1*	227.0***	97.0**
	(42.7)	(37.1)	(60.7)	(31.5)
N	897,852	897,852	897,852	897,852
Mean	129.3	95.6	250.6	74.8

Notes: Coefficients and Standard errors scaled to per 100,000 children. Births between 2000 and 2022. Regressions include mother fixed effects, year by month of birth fixed effects, and a female indicator. The mean of the dependent variable is displayed at the bottom of the table. Standard errors in parentheses are clustered at the mother level. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Effects of birth order on infant hospitalisations for infectious diseases

- large effects of birth orders on pertussis and influenza hospitalisations
- are infections higher *because* of lower maternal immunisations?
  - can't be the (only) explanation:
  - even before maternal immunisation was available, there are some birth order effects
  - birth order effects for infant hospitalisations due to RSV
- is it because of worse general health of later born?
  - no, they have higher birth weight
- 'contagion effect': having older siblings increases exposure
- is it *enough* to immunise older siblings? No!
  - restrict the sample to first-born children and later-born children whose older siblings were fully immunised at 12 months
  - means they received three doses of the 6-in-1 vaccine that include pertussis

Summary & discussion

- large decrease of uptake of maternal immunisations with each subsequent pregnancy
- three-fold disadvantage for later-born children
  - lower uptake of maternal immunisation
  - lower uptake of childhood immunisations
  - increased exposure to infectious diseases
- infants who would benefit the most from protection tend to miss out most often
- work in progress
  - heterogeneity analysis by child/family characteristics
  - robustness checks: controlling for health-at-birth, age of mother
  - effects on mother? hospitalisation during pregnancy by birth order
  - (covid vaccine?)

Thank you!

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Effects of birth order on RSV hospitalisations

	RSV hospitalisation	
	(1) ≤12 months	(2) ≤3 months
Birth order 2	1237.7***	846.2***
	(43.8)	(29.6)
Birth order 3	1827.3***	1201.8***
	(85.0)	(57.8)
Birth order 4	2538.4***	1594.1***
	(139.0)	(92.2)
N	897,852	897,852
Mean	1665.3	792.2

Notes: Regressions include mother fixed effects, year by month of birth fixed effects, and a female indicator. The mean of the dependent variable is displayed at the bottom of the table. Standard errors in parentheses are clustered at the mother level. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

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Mothers believe immunisation during previous pregnancy is enough

	(1) Maternal Tdap	(2) Maternal Influenza
Birth order 2	-0.463^{***}	-0.498^{***}
	(0.014)	(0.015)
Birth order 3	-0.513^{***}	-0.531^{***}
	(0.026)	(0.027)
N	15,243	11,724

Notes: Sample of families where the mother received immunisation during first pregnancy. Regressions include mother fixed effects, year by month of birth fixed effects, and a female indicator. The mean of the dependent variable is displayed at the bottom of the table. Standard errors in parentheses are clustered at the mother level. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

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Birth order effects when controlling for additional factors

	(1) Maternal Tdap	(2) Maternal Influenza	(3) Maternal Tdap	(4) Maternal Influenza
Birth order 2	-0.071^{***}	-0.014^{**}	-0.071^{***}	-0.016^{**}
	(0.005)	(0.005)	(0.006)	(0.006)
Birth order 3	-0.114^{***}	-0.040^{***}	-0.108^{***}	-0.042^{***}
	(0.009)	(0.009)	(0.012)	(0.011)
Birth order 4	-0.157^{***}	-0.107^{***}	-0.142^{***}	-0.072^{***}
	(0.015)	(0.015)	(0.022)	(0.021)
Previous pregnancy hospitalisation	-0.007	-0.009^{*}		
	(0.004)	(0.004)		
LMC visits during pregnancy			0.003^{***}	0.002^{***}
			(0.000)	(0.000)
N	152,142	152,142	108,918	108,918

Notes:Regressions include mother fixed effects, year by month of birth fixed effects, and a female indicator. The mean of the dependent variable is displayed at the bottom of the table. Standard errors in parentheses are clustered at the mother level. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

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Birth order effects on other outcomes

	LMC visits				Ultrasounds
	(1) 1^{st} trimester	(2) 2^{nd} trimester	(3) 3^{rd} trimester	(4) Total	(5)
Birth order 2	-0.052^{***}	-0.103^{***}	-0.455^{***}	-0.562^{***}	-0.218^{***}
	(0.006)	(0.009)	(0.016)	(0.022)	(0.006)
Birth order 3	-0.170^{***}	-0.179^{***}	-0.613^{***}	-0.914^{***}	-0.469^{***}
	(0.012)	(0.018)	(0.030)	(0.041)	(0.011)
Birth order 4	-0.317^{***}	-0.322^{***}	-0.781^{***}	-1.373^{***}	-0.840^{***}
	(0.020)	(0.029)	(0.047)	(0.066)	(0.018)
N	353,877	353,880	371,676	381,057	659,412
Mean	1.158	2.317	6.297	9.504	3.504

Notes:Regressions include mother fixed effects, year by month of birth fixed effects, and a female indicator. The mean of the dependent variable is displayed at the bottom of the table. Standard errors in parentheses are clustered at the mother level. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

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Effects of birth order on birth weight

	Birth weight
Birth order 2	147.909***
	(1.441)
Birth order 3	194.025***
	(2.544)
Birth order 4	236.445***
	(4.034)
N	1,037,655
Mean	3466.307

Notes: Regressions include mother fixed effects, year by month of birth fixed effects, and a female indicator. The mean of the dependent variable is displayed at the bottom of the table. Standard errors in parentheses are clustered at the mother level. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

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Fully immunised siblings

	Pertussis	
	(1) ≤12 months	(2) ≤3 months
Birth order 2	59.8***	46.1**
	(17.1)	(14.7)
Birth order 3	90.1**	79.9**
	(34.9)	(30.1)
Birth order 4	111.1	74.3
	(57.7)	(48.3)
N	503,601	503,601
Mean	94.1	72.7

Notes: Regressions include mother fixed effects, year by month of birth fixed effects, and a female indicator. The mean of the dependent variable is displayed at the bottom of the table. Standard errors in parentheses are clustered at the mother level. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

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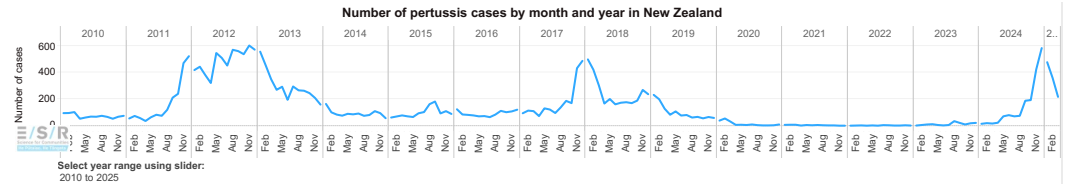
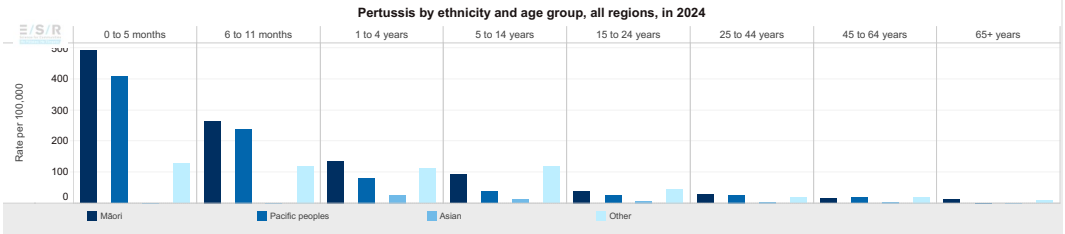
Pertussis infections - NZ surveillance data





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