

Influenza Hospitalizations during Childhood in Children born Preterm

Data availability statement: Data used in this manuscript are available for other researchers by standard application to the registries. Disclaimer. Data from the Norwegian Patient Registry have been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended nor should be inferred.

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Title:**Influenza Hospitalizations during Childhood in Children born Preterm****Short running title: Preterm birth and influenza hospitalizations**

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Abstract

Objective: To determine if children born preterm were at increased risk of influenza hospitalization up to age five.

Methods: National registry data on all children born in Norway between 2008 and 2011 was used in Cox regression models to estimate adjusted hazard ratios (aHR) for influenza hospitalizations up to age five in children born preterm (<37 pregnancy weeks). HRs were also estimated separately for very preterm (<32 weeks), early term (37-38 weeks), and post-term (≥42 weeks) children.

Results: Among 238 628 children born in Norway from January 2008 to December 2011, 15 086 (6.3%) were born preterm. There were 754 (0.3%) children hospitalized with influenza before age five. The rate of hospitalizations in children born preterm was 1.4 per 10 000 person-years (95% confidence interval [CI]: 1.1-1.7), and 0.6 per 10 000 person-years (95% CI: 0.5-0.6) in children born at term (≥37 weeks). Children born preterm had a higher risk of influenza hospitalization before age 5: aHR 2.33 (95% CI: 1.85-2.93). The risk increased with decreasing gestational age and was highest among those born very preterm; aHR 4.07 (95% CI: 2.63-6.31). Compared to children born at 40-41 weeks, children born early term also had an elevated risk of influenza hospitalization; aHR (37 weeks) 1.89 (95% CI: 1.43-2.40), aHR (38 weeks) 1.43 (95% CI: 1.15-1.78).

Conclusion: Children born preterm had a higher risk of influenza hospitalizations before age five. An elevated risk was also present among children born at an early term. Children born preterm would benefit from influenza vaccinations.

Keywords: Influenza human, infant premature, hospitalization.

1 Introduction

2 Annual influenza outbreaks cause severe and fatal infections in children worldwide, and children are
3 at higher risk of influenza hospitalization compared to many other age groups [1, 2]. To reduce the
4 risk of severe influenza disease and influenza deaths, the World Health Organization (WHO)
5 recommends risk groups to receive an annual influenza vaccine. Both the WHO and the US Centre
6 for Disease Control (CDC) include children younger than 5 years as a priority group for influenza
7 vaccination, however being preterm is not recognized as an additional risk factor [3, 4]. In tropical
8 and subtropical countries, national guidelines for prioritizing influenza vaccines are often absent [5].
9 In Norway, children in general are not included in the annual influenza vaccination program. Only
10 children with risk conditions, such as lung and heart disease, diabetes, neurological conditions, renal
11 or liver failure or immuno-compromised disorders are recommended the annual influenza
12 vaccination. Being born preterm is not identified as a risk condition in Norway [6].

13 The WHO defines preterm birth as children born before 37 completed weeks of gestation, and
14 globally more than 10% of live births, around 15 million children every year, are estimated to be
15 born preterm [7, 8]. These births are associated with substantial morbidity, and one million deaths a
16 year have been attributed preterm birth [9]. There is a disproportionately higher burden of preterm
17 births in low- and middle-income countries. High-income countries tend to have lower rates, though
18 in some high-income countries s, such as Austria and the USA, the proportion of preterm births is
19 higher than 10% [10, 11]. Norway has one of the lowest preterm birth rates in the world (5.6%) [12].
20 Established maternal risk factors for preterm birth include African-American/African-Caribbean
21 ethnicity, low or high maternal age, multiple pregnancy, maternal infections and low socioeconomic
22 status [13]. Improved treatment has increased the chance of survival in preterm infants, particularly
23 for those born extremely preterm (before 28 weeks) [14, 15]. Increased survival, combined with a
24 continuing high - and for some increasing - proportion of preterm births in many countries, has led to
25 an growing number of children in the population who were born preterm [10, 16, 17].

For all children, and especially those born preterm, respiratory tract infections cause a substantial number of hospitalizations and fatalities during the first years of life [9, 18-21]. Children born preterm have higher overall morbidity and mortality [22], and an increased risk of hospitalizations due to infections [23, 24]. Previous studies focusing on preterm birth as a potential risk factor for infections have mostly focused on hospitalizations with respiratory infections overall or respiratory syncytial virus (RSV) infections, and not on influenza [18, 25-28]. There is a scarcity of studies investigating influenza hospitalizations among preterm children beyond infancy, and currently insufficient evidence to implement vaccine recommendations for this group. In addition, it is not known to what extent risk differs with different gestational lengths, and whether children born early term also may be at higher risk.

Our aim was to assess whether children born preterm or early term were at increased risk of being hospitalized with influenza in the first five years of life. By including being born preterm as a risk factor for severe influenza beyond infancy could inform decisions on including these children in annual influenza vaccination programs around the world.

Methods

We included all children born in Norway between January 1, 2008 and December 31, 2011, and followed them to age five. We used data from two national health registries in Norway: the Medical Birth Registry of Norway (MBRN) [29] and the Norwegian Patient Registry (NPR) [30, 31]. The MBRN contains individual data on all births in Norway, and we used information on gestational age at birth, sex, season of birth, multiple births, maternal age at delivery, parity, and maternal smoking in pregnancy. Parental educational status was obtained from Statistics Norway, and categorized according to the highest completed academic level for either parent in 2013). The NPR holds data on ICD-10 diagnoses for all hospitalizations in Norway and reporting to NPR is mandatory. From the NPR, we collected data on hospital admissions with an influenza diagnosis for all children in the first

50 five years of life. Data were linked across registries using Norwegian personal identification
 51 numbers.

52 **Gestational age**

53 Completed gestational weeks at birth is recorded by the MBRN and based on routine ultrasound
 54 measurements when this was available (for 98% of the children), or last menstrual period when
 55 ultrasound estimations were missing. We categorized gestational age at birth into term (≥ 37
 56 completed weeks) or preterm (< 37 weeks), with the latter category additionally subdivided into
 57 extremely/very preterm (< 32 weeks) and moderately/late preterm (32 to < 37 weeks). The reference
 58 category was term births (≥ 37 weeks). To assess potential risks within the ‘term’ category,
 59 gestational age was further divided into eight categories (< 33 , 33-34, 35-36, 37, 38, 39, 40-41, ≥ 42),
 60 with 40-41 weeks as the reference category.

61 **Influenza hospitalizations**

62 An influenza hospitalization was defined as any hospitalization recorded on the NPR with the codes
 63 J09 (“Influenza due to identified zoonotic or pandemic influenza virus”), J10 (“Influenza due to
 64 identified seasonal influenza virus”) or J11 (“Influenza, virus not identified”) as listed in the 10th
 65 revision of the International Statistical Classification of Diseases (ICD-10). In ICD-10, laboratory
 66 confirmation is required for the J09 and the J10 diagnoses, but not for the J11 diagnose. To reduce
 67 potential misclassification, we excluded hospital admissions outside the yearly influenza surveillance
 68 period in Norway (running from October to May). Details of data sources and categorizations are
 69 presented in Table S1.

70 We used Cox regression modelling to assess associations between gestational age at birth and
 71 hospital admission for influenza up to age 5, using age in days from birth as the underlying time
 72 metric. Children were followed from birth until the first influenza hospitalization, death, emigration,
 73 or their 5th birthday. In additional analyses, we estimated the risk of influenza hospitalization in three

different age groups (<1 year, 1 year, 2-4 years). A sensitivity analysis excluded multiple births. As potential confounders, we included child sex, maternal parity, maternal age, multiple birth, season of birth, parental education, and maternal smoking. We conducted complete case analyses and adjusted for these covariates in our models. Dependency between siblings was taken into account by the use of robust standard errors. The proportional hazards assumption was evaluated by visual inspection of cumulative hazard curves and by testing Schoenfeld residuals. Analysis was performed using Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

The Norwegian Regional Committee for Medicine and Health Research Ethics approved this study and provided a waiver of consent for participants.

83

84 **Results**

There were 245 281 children registered in the birth registry of Norway between January 1, 2008 and December 31, 2011. Less than 3% were excluded due to missing covariate information (n=4171) or invalid linkage (n=2482), leaving 238 628 children for analyses (Figure S1). In total, 15 086 (6.3%) of the children were born preterm (< 37 weeks). Of these, 12 941 (85.8%) moderate/late preterm (born between weeks 32 and 36) and 2145 (14.2%) were extremely/very preterm (born before 32 weeks gestation). Preterm children were more likely to be multiple births, male, first-born, and have a younger or older mother, and a mother who smoked during pregnancy; and less likely to have at least one parent with college or university education (Table 1).

Overall, 754 (0.3%) children were hospitalized with influenza below the age of five (Table S2). Of these, 101 (13.4%) were born preterm. Compared to children born at term, the cumulative incidence of hospital admission with influenza was higher in children born preterm (Figure 1a), and even higher among very preterm infants (Figure 1b). The rate in preterm children was 1.4 per 10 000 person-years (95% confidence interval (CI) 1.1-1.7), while in term children the rate was 0.6 per 10 000 person-years (95% CI 0.5-0.6). Compared to term children, the adjusted hazard ratio for

99 hospitalization before age five in children born preterm was 2.33 (95% CI 1.85-2.93) (Table 2).

100 Stratifying by age at follow-up, the increased risk of influenza hospitalization for preterm born

101 children compared to term children was similar across all age periods (<1 year aHR 2.24, 95% CI

102 1.44-3.50; 1-<2 years aHR 2.26, 95% CI 1.58-3.25; 2-<5 years aHR 2.47, 95% CI 1.66-3.66; Table

103 S3).

104 Children born moderately or late preterm (32-37 weeks) had a higher risk of hospitalization

105 compared to those born at term (aHR 2.06, 95% CI 1.60-2.67), and those born <32 weeks (extremely

106 or very preterm) had a fourfold higher risk of hospital admission for influenza (aHR 4.06, 95% CI

107 2.62-6.29) (Table 2) compared to children born at term.

108 When stratifying gestational age at birth into 1 or 2-week categories, the risk of hospital admission

109 for influenza increased with decreasing gestational age (Table 3). Compared to children born at 40-

110 41 weeks, children born late preterm (35-36 weeks, n=8 854) had a higher risk of hospitalization

111 (aHR 2.18, 95% CI 1.59-3.00). Among children born at term, 42 530 (19%) were born at 37 or 38

112 weeks (defined as 'early term'). Compared to children born at 40-41 weeks, these early term children

113 also had an elevated risk of hospital admission for influenza (aHR for 37 weeks 1.89, 95% CI 1.43-

114 2.50; aHR for 38 weeks 1.43, 95% CI 1.15-1.78). The cumulative incidence of hospital admission for

115 influenza for children born post-term (≥ 42 weeks, n=13,702) was slightly higher (6.5 per 10 000

116 person-years compared to 5.3 for children born 40-41 weeks), though this difference was not

117 significant (aHR of 1.25, 95% 0.91-1.72).

118 Preterm birth is common in multiple pregnancies. To exclude the possibility that multiple births were

119 driving the observed associations between preterm birth and influenza, we repeated our main

120 analysis after excluding multiple births. The results were almost identical to the results with

121 multiples included (aHR for singletons only: 2.36; 95% CI: 1.86-2.99, Table S4).

122

123 Discussion

124 Our results show that children who were born preterm had a higher risk of hospitalization with
125 influenza up to age five. The increased risk was apparent also for children born early term, and the
126 risk increased with each week of shorter gestational age. Children born extremely preterm (<32
127 weeks) had a more than fourfold risk of hospitalization with influenza in the first five years of life
128 compared to those born at term.

129 In our study 6.3% of the children were born preterm (<37 weeks), corresponding to 5.6% of
130 pregnancies, as many multiples are born preterm. This is similar to rates in other Nordic countries,
131 which have preterm rates of 5.6% (Sweden, 2001) [32], 6.3% (Denmark, 2004) [17] and 5.2%
132 (Finland, 2001-05) [33].

133 Our results support previous studies finding that lower gestational age is associated with an increased
134 risk of hospital admissions due to respiratory infections, and that risk of infection increase with lower
135 gestational age [19, 34]. A systematic review investigated a range of risk factors for children
136 hospitalized with influenza and concluded that prematurity was one of the most important risk
137 factors [35]. However, five of the seven studies included in this review did not define prematurity in
138 terms of gestational age, and they were unable to assess the risk beyond the first two years of life.
139 With the lack of supporting evidence, preterm children are still not defined as a risk group and
140 prioritized for influenza vaccination.

141 Increased susceptibility to severe influenza could partly be explained by sequelae and comorbidities
142 associated with preterm birth [22]. Neonates and preterm infants even more so, have an immature
143 immune system in the first months of life. Fetal lungs develop gradually and preterm birth interrupts
144 the normal maturing process, but also additional factors contribute to the increased susceptibility for
145 infections [36, 37]. An estimated 40% of children born extremely preterm develop sequelae
146 including bronco-pulmonary dysplasia (BPD) [38], which is observed to cause reduced respiratory

147 function that persist into late adolescence and adulthood [39, 40]. Increasingly lower gestational age
148 is associated with reduced lung function [41].

149 Previous research primarily reports an increased risk for severe influenza for children born
150 moderately to extremely preterm. These studies lacked sufficient detail to assess the association
151 between the extent of prematurity and risk of hospital admission, and the need for further studies has
152 been emphasized [35]. Some researchers have addressed overall respiratory morbidity among those
153 born moderately/late preterm and early term. Findings support an increased risk for respiratory
154 hospitalization for those both born late preterm (35-36 weeks) and even early term (37-38 weeks),
155 but these studies have not addressed risk of influenza hospitalizations in particular [42-46].
156 Sequelae (such as reduced lung function) which is known to increase the risk of severe influenza but
157 is only present in a minority of preterm children. The majority; also those born extremely preterm,
158 have no known bronchopulmonary dysplasia later in life [38]. The increased risk of influenza
159 hospitalization we found in this study among the early term and late preterm is therefore not likely to
160 be explained by long-term respiratory-related sequela.

161 All registry-based studies are prone to some misclassification. According to the ICD-10 diagnostic
162 guidelines, laboratory testing for influenza was not required for all the ICD-10-diagnoses we used to
163 define hospitalizations with influenza. In the absence of laboratory confirmation, recording of an
164 influenza diagnosis depends on the clinician's judgement of the clinical symptoms and patient
165 history and therefore may be incorrect. However, 83% of the influenza hospitalizations included in
166 our study were associated with ICD-10 J09 or J10 diagnosis, which requires laboratory confirmation.
167 Previous studies have found that ICD-10 data underestimate rather than overestimate the numbers of
168 influenza cases, with a high specificity for influenza diagnoses [47]. Data on laboratory testing for
169 seasonal influenza is not recorded in national registries, and we did not have information on
170 laboratory testing in our study. We aimed to reduce potential misclassification of influenza diagnoses
171 by excluding hospitalizations outside the influenza surveillance period. It may be that children who

172 were born preterm and are admitted to hospitals with influenza symptoms are disproportionately
173 likely to be tested and diagnosed with influenza, causing a potential inflation of association.
174 However, we believe that preterm birth is less likely to be considered a key patient characteristic
175 when treating children for influenza beyond the infant period, and also that most children with
176 symptoms will have been tested (irrespective of preterm status).

177 We were able to stratify preterm births into extremely/very preterm (<32 weeks) and moderately/late
178 preterm. However, we were unable to further stratify the former category into extremely or very
179 preterm for anything other than descriptive analysis due to small cell counts.

180 Although preterm birth is highly correlated with low birth weight, our aim was to address the total
181 effect of being born preterm (which includes lower birth weight) rather than assessing the
182 independent effects of gestational age and birthweight, which are difficult to disentangle [48].

183 We did not include data on the vaccination status of the child or the mother in our study. However, in
184 Norway, children in general are not classified as a priority group for influenza vaccination. Although
185 children with chronic diseases are recommended for the annual influenza vaccine, survey data from
186 Norway indicates that vaccination coverage is far from optimal, with only around 39% coverage in
187 high risk groups (all ages) in 2018-19 [49]. Therefore, it is likely that only a small proportion of
188 children in Norway have received the annual influenza vaccination during the study period, and it is
189 likely that children who received vaccination had higher underlying susceptibility to infection due to
190 other risk factors. Equally, some infants may have received some protection in the first months after
191 birth via maternal immunization during the in utero period. However, uptake of influenza vaccination
192 during pregnancy in Norway is low [50], and protection conferred by maternal vaccination is not
193 likely to persist past the infant period [51].

194 **Conclusion**

195 Children born preterm were at increased risk of hospitalization with influenza infection during their
196 first five years of life. This risk increased with decreasing gestational age at birth and was fourfold
197 for children born before 32 weeks of gestation. The risk of hospitalization for influenza was also
198 higher in children born at an early term gestation compared to children born in gestational week 40
199 and 41. Our results support the inclusion of children who were born preterm as a risk group in the
200 seasonal influenza vaccination programs to reduce severe influenza infections and hospitalizations in
201 this high-risk group. In settings where children are already included in routine influenza vaccination
202 programs, vaccine hesitancy is still an obstacle [52] and efforts should be made to communicate the
203 importance of influenza vaccination in this high-risk group of children.

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326 **Figure 1. Cumulative incidence of influenza hospitalization to age 5, by (a) preterm status**
 327 **(preterm, term) and (b) preterm group (extremely/very preterm, moderate/late preterm, term)**

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331 **Table 1. Perinatal and child characteristics of children born between January 1 2008 and**
 332 **December 31 2011 in Norway**

	All children	Preterm (<37 weeks)		Influenza hospitalization <5 years	
	n	n	(%)	n	(%)
All children	238 628	15 086	(6.3)	754	(0.3)
Maternal age at birth					
<20	5 208	437	(8.4)	23	(0.4)
20-24	34 672	2 272	(6.6)	99	(0.3)
25-29	74 101	4 287	(5.8)	224	(0.3)
30-34	77 697	4 587	(5.9)	251	(0.3)
35-39	39 416	2 802	(7.1)	137	(0.3)
≥40	7 534	701	(9.3)	20	(0.3)
Maternal smoking in pregnancy					
No	179 883	10 954	(6.1)	536	(0.3)
Yes	24 496	1 930	(7.9)	106	(0.4)
Information declined	34 249	2 202	(6.4)	112	(0.3)
Child sex					
Male	122 749	8 083	(6.6)	447	(0.4)
Female	115 879	7 003	(6.0)	307	(0.3)
Birth order					
1	101 747	7 374	(7.2)	258	(0.3)
≥2	136 881	7 712	(5.6)	496	(0.4)
Multiple birth					
Yes	7 872	3 758	(47.7)	37	(0.5)
No	230 756	11 328	(4.9)	717	(0.3)
Parental college/university education					
No	95 780	6 697	(7.0)	352	(0.5)
Yes	142 848	8 389	(5.9)	402	(0.2)
Season of birth					
Winter	54 943	3 741	(6.8)	158	(0.3)
Spring	61 212	3 783	(6.2)	178	(0.3)
Summer	63 979	4 018	(6.3)	201	(0.3)
Autumn	58 494	3 544	(6.1)	217	(0.3)

333

334 **Table 2. Association between gestational age category and influenza hospitalization before age**
 335 **5 years**

	<i>No. of children</i>	<i>No. of person-years at risk</i>	<i>No. of influenza cases</i>	<i>Hazard ratio (95% CI)*</i>	
				Unadjusted	Adjusted
<i>Total number of children</i>	238 628	1 180 599	754		
<i>Gestation at birth</i>					
<i>Term (≥37 weeks)</i>	223 542	1 107 171	653	ref	ref
<i>Preterm (<37 weeks)</i>	15 086	73 427	101	2.33 (1.88-2.89)	2.33 (1.85-2.93)
<i>Extremely/very preterm (<32 weeks)</i>	2 145	9 722	23	4.00 (2.60-6.17)	4.07 (2.63-6.31)
<i>Moderate/late preterm (32-<37 weeks)</i>	12 941	63 706	78	2.08 (1.63-2.65)	2.07 (1.60-2.68)

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337 *Adjusted for season of birth, sex, maternal age, multiple birth, maternal smoking, birth order,
 338 parental educational level

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342 **Table 3. Association between gestation (by week) and influenza hospitalization before age 5**
 343 **years**

	<i>No. of children</i>	<i>No. of person- years at risk</i>	<i>No. of influenza cases</i>	<i>Hazard ratio (95% CI)*</i>	
				Unadjusted	Adjusted
Total number of children	238 628	1 180 599	754		
Gestation at birth					
<33 weeks	2 966	13 708	29	4.01 (2.68-6.02)	4.25 (2.83-6.37)
33 - 34 weeks	3 266	16 051	23	2.73 (1.76-4.24)	2.84 (1.82-4.42)
35 - 36 weeks	8 854	43 669	49	2.13 (1.57-2.90)	2.18 (1.59-3.00)
37 weeks	12 453	61 599	61	1.88 (1.42-2.49)	1.89 (1.43-2.50)
38 weeks	30 077	148 847	114	1.46 (1.17-1.81)	1.43 (1.15-1.78)
39 weeks	54 373	269 338	140	0.99 (0.81-1.21)	0.98 (0.80-1.20)
40 - 41 weeks	112 937	559 572	294	ref	ref
42+ weeks	13 702	67 815	44	1.23 (0.90-1.69)	1.25 (0.91-1.72)

344 *Adjusted for season of birth, sex, maternal age, multiple birth, maternal smoking, birth order,
 345 parental educational level

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