Trends and Changes in Influenza-associated Hospitalizations in Children During 25 Years in Finland, 1993-2018

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ABSTRACT

Background

Limited long-term data are available on potential changes in the demographics and management of children hospitalized with influenza.

Methods

We identified all children aged ≤15 years hospitalized with virologically confirmed influenza at Turku University Hospital, Finland, during the 25-year period of July 1993-June 2018. Data on clinical variables, comorbidities, and management were retrieved directly from the medical records. Population-based rates of hospitalization were calculated using official annual databases of children living in the hospital catchment area.

Results

Between 1993-1998 and 2013-2018, the median age of children increased from 1.3 years to 3.3 years (P<.0001). The proportion of children aged <2 years decreased from 65.2% to 36.8%, whereas the proportion of children aged 6-15 years increased from 13.0% to 36.2% (P<.0001 for both). The population-based rates of hospitalization decreased by 49% in children aged 1 year (incidence rate ratio [IRR], 0.51; 95% CI, 0.27-0.92; P=.018) and increased by 194% in children aged 6-15 years (IRR, 2.94; 95% CI, 1.70-5.32; P<.0001). The median duration of hospitalization shortened from 2.0 days (interquartile range [IQR], 1.0-4.0) to 1.0 day (IQR, 1.0-2.0; P<.0001).

Conclusions

During the 25 years, the median age of hospitalized children increased by 2 years, while the duration of hospitalization shortened.

INTRODUCTION

Influenza viruses continue to infect millions of children every year. According to a recent global estimate, approximately 110 million episodes of influenza occurred in children under 5 years in 2018 (1). Despite many important advances seen in the field of influenza, influenza-associated hospitalizations are still common in children, and the highest rates are invariably reported among infants <6 months of age (2-4).

During the past several years, the measures available for prevention, treatment, and diagnosis of influenza have expanded substantially. Current influenza vaccines have largely switched from trivalent to quadrivalent vaccines that can provide increased coverage against circulating strains of influenza, and new technologies to improve vaccine efficacy have been adopted (5). The development of intranasally administered vaccines has offered an alternative way of vaccination especially for children. Several antiviral agents against influenza have been produced, with orally administered oseltamivir being most widely used and available to children of any age (6). When started early in the course of influenza, oseltamivir treatment effectively shortens the duration of illness and reduces both influenza symptoms and the development of the most frequent complications (7-9).

Despite improvements in influenza vaccines and increased recommendations to vaccinate all young children (3, 10, 11), the vaccination rates of children remain low in many countries (12, 13). Because in any case none of the current vaccines is indicated for infants <6 months of age, vaccination of mothers during pregnancy has been introduced as a way to protect the very youngest infants and has been shown efficacy in clinical trials (14).

The virologic diagnosis of influenza has become faster and easier with the development of various rapid tests involving antigen detection and polymerase chain reaction methods (15). These tests allow for the diagnosis of influenza at almost any medical facility, and they have become part of everyday diagnostics in emergency clinics.

While major developments in the influenza field have provided us with new possibilities to reduce the burden of influenza in children, little is known about potential changes in the demographics and management of children hospitalized with influenza during the past decades. The aim of this study was to investigate trends and changes in influenza-associated hospitalizations of children during a period of 25 years.

METHODS

Study Design and Population

This retrospective study was conducted at the Department of Pediatrics, Turku University Hospital, Finland, during the 25-year period of July 1, 1993, through June 30, 2018. The study population consisted of all children ≤15 years of age who were hospitalized with virologically confirmed influenza A or B infection at Turku University Hospital that is the only tertiary-care hospital in Southwestern Finland and the sole provider of acute pediatric hospital care for children. To allow for reliable estimation of population-based rates of hospitalization, only children whose place of residence was within the catchment area of the hospital were included in the study. Detailed annual data on the numbers of children in different age cohorts were obtained from the official databases of Statistics Finland. During the 25-year study period, the average population of children ≤15 years of age living in the catchment area of the hospital was 70,890.

Sources of Data

To find all children hospitalized with virologically confirmed influenza, we searched the database of the Department of Virology, University of Turku, the central database of Turku University Hospital, and the databases and files of the pediatric intensive care unit and the pediatric infectious diseases ward. The medical records of all children with an International Classification of Diseases (ICD) code related to influenza (ICD-9: 4870A, 4871A, 4878X; ICD-10: J10-J11) who were not included in the virologic databases were carefully examined to confirm or rule out the viral diagnosis of influenza. Data on clinical variables,

comorbidities, management, and outcomes were collected by a systematic review of the medical records. To rule out potential nosocomial infections, children whose viral specimens had been obtained >2 days after admission were excluded from the analyses. The final study population consisted of 703 children.

Virologic Methods

Viral sampling for the identification of respiratory viruses was routine for all children hospitalized with respiratory symptoms during the study period. The virologic diagnosis of influenza was made at the Department of Virology by RT-PCR, antigen detection, or viral culture in 483 (68.7%) cases, and at the hospital emergency department or wards by antigen detection in 209 (29.7%) cases; in 11 (1.6%) cases, the exact method of viral diagnosis remained undetermined.

Definitions

Children were considered to have an underlying risk condition for severe influenza if they had a pulmonary, cardiac, endocrine, liver, kidney, or major neurologic disorder or malignancy or other immunosuppressive condition documented in the medical chart. The length of hospital stay was recorded as the number of nights spent on the ward. In case a child was admitted in the morning and discharged in the evening of the same day, the length of hospital stay was recorded as 1 day. Each study year was defined as the period from July 1 through June 30 of the following year. To analyze any trends during the study period, the 25-year period was divided into 5 consecutive 5-year periods. The children were classified into 6 age groups (<6 and 6-11 months and 1, 2, 3-5 and 6-15 years) on basis of their age on the day of admission. The age categorization of children younger than 3 years was based on previously available data on pronounced differences in population-based incidence of influenza-associated hospitalization between those age groups (2).

Statistical Analyses

The incidence rates of influenza hospitalizations were calculated by dividing the numbers of hospitalizations

by the numbers of children at risk and expressed per 100,000 children. Confidence intervals (CIs) for incidence rates and their ratios and testing of the differences in incidence rates were based on the Poisson distribution. Comparison of medians between the different 5-year periods was performed by the Kruskal-Wallis test, and proportions were compared by the χ^2 test. P values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using StatsDirect software, version 3.3.4 (StatsDirect).

RESULTS

Study Population

A total of 703 children with laboratory-confirmed influenza were hospitalized during the 25-year study period. Of these, 137 (19.5%) were infants <6 months of age and 221 (31.4%) were <1 year of age (Table 1). Boys accounted for 394 (56.0%) of all hospitalizations. Influenza A was detected in 536 (76.2%) children and influenza B in 159 (22.6%) children; 8 (1.1%) children had both A and B viruses simultaneously (Figure 1). At least one risk condition for severe influenza was present in 176 (25.0%) children, and the prevalence of such conditions increased with age. At admission, a septic illness was clinically suspected in 57 (41.6%) of infants <6 months of age and in 103 (14.7%) of all children. A total of 372 (52.9%) children received antibiotic treatment during the hospitalization. Seventy-four (10.5%) children were treated at the intensive care unit, and 2 (0.3%) children died.

Influenza in Different Age Groups

During the 25-year study period, the average annual population-based incidence rate of influenza-related hospitalization was highest among infants <6 months of age (259 per 100,000; 95% CI: 217-306), followed by infants 6-11 months of age (159 per 100,000; 95% CI: 127-196). The incidence rate among all infants <1 year of age was 209 per 100,000 (95% CI: 182-238). In the entire group of children up to 15 years of age, the annual incidence rate was 40 per 100,000 (95% CI: 37-43).

During the consecutive 5-year periods, the overall incidence rates of hospitalization in children up to 15 years of age ranged between 34-43 per 100,000, with no significant trends towards increase or decrease. However, in the youngest age groups, the incidence rates showed decreasing trends during the study period (Figure 2). Compared with the 5-year period of 1993-1998, the incidence rates in 2013-2018 were 27% lower both in infants <6 months of age (incidence rate ratio [IRR], 0.73; 95% CI: 0.42-1.27; P=0.24) and in those aged 6-11 months (IRR, 0.73; 95% CI: 0.34-1.51; P=0.35). Among children 1 year of age, the corresponding 49% decrease was statistically significant (IRR, 0.51; 95% CI: 0.27-0.92; P=0.018). In contrast with the youngest children, there was a significant increase in the incidence rate among children 6-15 years of age during the same periods (IRR, 2.94; 95% CI: 1.70-5.32; P<0.0001).

The median age of hospitalized children during the entire study period was 2.2 years (interquartile range [IQR], 0.7-6.6). The median age at admission increased significantly during the study period, from 1.3 years (IQR, 0.5-2.8) in 1993-1998 to 3.3 years (IQR, 1.0-9.2) in 2013-2018 (P<0.0001; Table 2). The changes in the relative proportions of different age groups during the study period are shown in Figure 3. The proportion of children <2 years of age decreased from 65.2% in 1993-1998 to 36.8% in 2013-2018, whereas the proportion of children 6-15 years of age increased from 13.0% to 36.2% between the corresponding periods (P<0.0001 for both comparisons).

Influenza in Boys and Girls

The average annual incidence rate of influenza hospitalization during the 25-year study period was 43 per 100,000 (95% CI: 39-48) in boys and 36 per 100,000 (95% CI: 32-40) in girls (IRR, 1.21; 95% CI: 1.04-1.41; P=0.01). The incidence rates were higher in boys than in girls in all age groups, although the differences within the specific age groups did not reach statistical significance (see Figure, Supplemental Digital Content 1).

Length of Stay and Intensive Care Treatment

The median duration of hospitalization during the 25-year study period was 2.0 days (IQR, 1.0-3.0). The median length of stay shortened from 2.0 days (IQR, 1.0-4.0) in 1993-1998 to 1.0 day (IQR, 1.0-2.0) in 2013-2018 (P<0.0001; Table 2). There were no statistically significant differences in the length of stay between boys and girls and between different age groups. The proportions of children treated at the intensive care unit varied between 6.5% and 15.1% during the study period, with no significant trends between the consecutive 5-year periods (Table 2).

Clinical Suspicion of Sepsis

The clinical suspicion of sepsis at admission decreased towards the end of the study period (Table 2). Between 1993 and 2003, 15.9-20.3% of children were suspected of having a septic infection, compared with 7.2% in 2013-2018 (P=0.005 for trend). There were no differences in clinical suspicion of sepsis between boys and girls.

Antibiotic Treatment

Among all children, treatment with antibiotics decreased from 55.8% in 1993-1998 to 45.4% in 2003-2018 (P=0.008 for trend; Table 2). No significant changes were observed within any age-specific subgroups of children.

Risk Conditions for Severe Influenza

The proportions of children with underlying risk conditions for severe influenza increased during the study period from 17.4% in 1993-1998 to 30.9% in 2013-2018 (P=0.02 for trend; Table 2). No differences in the presence of risk conditions were observed between boys and girls.

Influenza as Discharge Diagnosis

Overall, 533 (75.8%) of the 703 hospitalized children had an ICD code related to influenza in their medical records. The proportion of such ICD codes was lowest (61.6%) during 1993-1998 but increased to 80.2-83.3% during the last two 5-year periods (P<0.0001 for trend; Table 2).

DISCUSSION

Our analysis of pediatric influenza hospitalizations during a 25-year period revealed significant changes in the demographics, management, and clinical features of admitted children. Perhaps most interestingly, there was a fundamental shift in the age spectrum of hospitalized children, with the median age of children increasing gradually during the study period. Between the first and the last 5-year periods, the relative proportion of children <2 years of age almost halved, while the proportion of children 6-15 years of age almost tripled. Of note, the overall incidence rate of influenza hospitalization among all children stayed rather constant during the study period.

The shift in the relative proportions of different age groups was accompanied by changes in the absolute population-based incidence rates of hospitalization in different age groups. Although throughout the study period the incidence of influenza-related hospitalization remained clearly highest among infants <6 months of age, there were clear trends towards decreasing hospitalization rates among all children <2 years of age. By contrast, the population-based incidence rate of hospitalization among children 6-15 years of age increased by 3-fold during the 25 years of the study.

Several factors may contribute to the observed changes in the age of hospitalized children. One potential explanation could be the increasing availability and use of rapid diagnostics of influenza. As the clinical presentation of influenza is most severe in the youngest children, they are frequently admitted for follow-up to rule out septic infections (16, 17). Knowledge of influenza being the reason for high fever and other symptoms may help decrease the need for hospitalization in the emergency department or even the referral of children from outpatient offices. Our finding that the clinical suspicion of sepsis at admission

decreased significantly towards the end of the study period could also lend some support to the impact of rapid diagnosis of influenza. It could be hypothesized that in an era of improved rapid diagnostics, an overall decrease in all-cause hospitalization of febrile infants could explain the decreasing trends observed in the present study. However, an extensive US study appears to effectively oppose such an idea (18). Among 11,600 infants admitted between 2002-2012, admissions of febrile infants younger than 90 days actually increased statistically significantly by 3% during each year of the study despite advances in diagnostics and a generally lowered risk of serious bacterial infections in infants.

Influenza vaccination could be another factor behind the decreasing hospitalization rates among the youngest children. In Finland, influenza vaccination was included in the routine childhood immunization program for all children 6-35 months of age in 2007. A recent meta-analysis of the impact of influenza vaccination in preventing hospitalization due to influenza demonstrated a 53% effectiveness of vaccination against hospitalization in children (19). However, because in our study the rates of hospitalization among children <2 years of age had been already decreasing before the start of the vaccination program, it is likely that factors other than vaccination have contributed substantially to the decreasing hospitalization rates. The same applies to maternal influenza vaccination during pregnancy, which has been officially recommended in Finland only since 2010, i.e., long after the start of the declining trend in the hospitalization of infants <6 months of age who would be expected to benefit most from maternal vaccination.

The observed increase in the relative proportion of 6-15-year olds among all hospitalized children could be easily explained by the decreasing absolute rates of hospitalization among the younger children, but the 3-fold increase in the absolute rate of hospitalization among children 6-15 years of age is more difficult to explain. Further studies are needed to shed light on the potential reasons for this rather unexpected finding.

The population-based incidence rate of influenza hospitalization was approximately 20% higher in boys than in girls, and the difference towards the same direction was observed in all age groups. This finding is consistent with several previous studies reporting excess numbers of influenza hospitalizations in boys (2, 4, 20-22). While the underlying reasons are probably complex and remain largely unknown, boys appear to be at greater risk for severe influenza outcomes than girls. Proposed mechanisms include sex-dependent differences in innate and adaptive immune responses, viral loads, and time to clearance of viruses (23).

The median duration of hospitalization shortened significantly from 2 days to 1 day during the study period. Although we could not reliably assess the use of antiviral treatments in the present study, it is tempting to speculate that increased use of antivirals in children hospitalized with influenza might have contributed to the shortened length of stay. Oseltamivir has been available for children since the early 2000s and for infants since 2012, and its use in hospitalized children has been widely recommended (6, 24). A recent study from the United States reported that between 2010-2011 and 2018-2019, the use of antiviral treatment in hospitalized children increased from 56% to 85% (4), and a similar increasing trend was observed also in a Canadian study during the same seasons (22). At our hospital, the use of oseltamivir has been routine for all hospitalized children since the early 2010s. Early administration of oseltamivir during the course of influenza illness not only shortens the duration of illness but also reduces the severity of symptoms, which might allow for faster discharge of children from hospital (7-9).

Approximately half of the hospitalized children were treated with antibiotics, and the frequency of antibiotic use was highest among children <3 years of age. These findings are in line with previous studies that have also demonstrated that 30-50% of antibiotic treatments in children hospitalized with influenza are given without proper evidence for a concomitant bacterial infection (25-27). In the present study, the use of antibiotics in all children reduced by 19% between the first and the last 5-year periods, although no significant changes could be demonstrated within any age-specific subgroups. Point-of-care influenza

testing has been shown to effectively reduce unnecessary antibiotic treatments (28), and increased use of rapid testing may have also contributed to the reduction in antibiotic use in our study.

Overall, 25% of hospitalized children in our study had an underlying risk condition, and the prevalence of such conditions increased with age. In a recent study from Norway, children with pre-existing risk conditions for severe influenza had a >6-fold higher risk of hospitalization than children without (29). Because the presence of underlying risk conditions increases with age (2, 4), this has undoubtedly also contributed to our observation about the shift towards older age groups being hospitalized.

The proportions of children who were discharged with an influenza-related ICD code increased significantly during the study period. Nevertheless, even during the last 5-year period, such ICD codes were present in only 80% of children with virologically confirmed influenza, which means that relying on influenza-related ICD codes would have missed every fifth child with true influenza-associated hospitalization. In line with our findings, a recent analysis of administrative data from 3 US hospitals yielded a sensitivity of 72.5% for influenza-specific discharge codes, although the specificity of such codes exceeded 99% (30).

The strengths of our study include the 25-year study period that allowed for identification of changes and trends that would be difficult to detect in studies with much shorter durations. Our study was conducted at a large hospital with a clearly defined catchment area, and annual numbers of children of different ages living in the area could be retrieved reliably from official databases. Of particular importance, sampling for influenza viruses was routine for all children hospitalized with respiratory symptoms throughout the years of the study. Although our study was conducted only at a single hospital, this minimized the potential variability in clinical practices between different hospitals and thus probably allowed for more precise estimation of changes occurring over time. As for limitations of the study, we did not have the possibility to systematically collect data on antiviral treatment in the children, and we could not have information about the influenza vaccination status of the hospitalized children.

In conclusion, the age distribution of children hospitalized with influenza has changed but the burden of influenza remains great. While the population-based incidence rates of hospitalization have decreased among the youngest children, the corresponding rates have increased in older children in whom underlying risk conditions are more prevalent. Despite important advances in influenza diagnostics, vaccination, and antiviral treatment during the past years, the hospitalization rates are still clearly highest among infants <6 months of age who are not eligible for influenza vaccination. Effective new strategies are needed to diminish the burden of influenza especially in the youngest infants.

REFERENCES

1. Wang X, Li Y, O'Brien KL, et al. Global burden of respiratory infections associated with seasonal influenza in children under 5 years in 2018: a systematic review and modelling study. *Lancet Glob Health.* 2020;8:e497-e510.
2. Silvennoinen H, Peltola V, Vainionpää R, Ruuskanen O, Heikkinen T. Incidence of influenza-related hospitalizations in different age groups of children in Finland: a 16-year study. *Pediatr Infect Dis J.* 2011;30:e24-e28.
3. Heikkinen T, Tsolia M, Finn A. Vaccination of healthy children against seasonal influenza: a European perspective. *Pediatr Infect Dis J.* 2013;32:881-888.
4. Kamidani S, Garg S, Rolfes MA, et al. Epidemiology, clinical characteristics, and outcomes of influenza-associated hospitalizations in US children over 9 seasons following the 2009 H1N1 pandemic. *Clin Infect Dis.* 2022 (available online 19 Apr 2022) https://doi.org/10.1093/cid/ciac296.
5. Khalil N, Bernstein DI. Influenza vaccines: where we are, where we are going. *Curr Opin Pediatr.* 2022;34:119-125.
6. Moodley A, Bradley JS, Kimberlin DW. Antiviral treatment of childhood influenza: an update. *Curr Opin Pediatr.* 2018;30:438-447.
7. Heinonen S, Silvennoinen H, Lehtinen P, et al. Early oseltamivir treatment of influenza in children 1–3 years of age: a randomized controlled trial. *Clin Infect Dis.* 2010;51:887-894.
8. Malosh RE, Martin ET, Heikkinen T, Brooks WA, Whitley RJ, Monto AS. Efficacy and safety of oseltamivir in children: systematic review and individual patient data meta-analysis of randomized controlled trials. *Clin Infect Dis.* 2018;66:1492-1500.
9. Mattila JM, Vuorinen T, Waris M, Antikainen P, Heikkinen T. Oseltamivir treatment of influenza A and B infections in infants. *Influenza Other Respir Viruses.* 2021;15:618-624.
10. Usonis V, Anca I, André F, et al. Central European Vaccination Advisory Group (CEVAG) guidance statement on recommendations for influenza vaccination in children. *BMC Infect Dis.* 2010;10:168.

11. World Health Organization. Vaccines against influenza: WHO position paper – May 2022. *Wkly Epidemiol Rec.* 2022;97:185-208. Available at: https://www.who.int/publications/i/item/who-wer9719 (accessed 23 August 2022)
12. McGuire A, Drummond M, Keeping S. Childhood and adolescent influenza vaccination in Europe: A review of current policies and recommendations for the future. *Expert Rev Vaccines.* 2016;15:659-670.
13. European Centre for Disease Prevention and Control. Seasonal influenza vaccination and antiviral use in EU/EEA Member States – Overview of vaccine recommendations for 2017–2018 and vaccination coverage rates for 2015–2016 and 2016–2017 influenza seasons. Available at: https://www.ecdc.europa.eu/en/publications-data/seasonal-influenza-vaccination-antiviral-use-eu-eea-member-states (accessed 23 August 2022).
14. Jarvis JR, Dorey RB, Warricker FDM, Alwan NA, Jones CE. The effectiveness of influenza vaccination in pregnancy in relation to child health outcomes: systematic review and meta-analysis. *Vaccine.* 2020;38:1601-1613.
15. Gentilotti E, De Nardo P, Cremonini E, et al. Diagnostic accuracy of point-of-care tests in acute community-acquired lower respiratory tract infections: a systematic review and meta-analysis. *Clin Microbiol Infect.* 2022;28:13-22.
16. Silvennoinen H, Peltola V, Lehtinen P, Vainionpää R, Heikkinen T. Clinical presentation of influenza in unselected children treated as outpatients. *Pediatr Infect Dis J.* 2009;28:372-375.
17. Silvennoinen H, Peltola V, Vainionpää R, Ruuskanen O, Heikkinen T. Admission diagnoses of children 0-16 years of age hospitalized with influenza. *Eur J Clin Microbiol Infect Dis.* 2012;31:225-231.
18. Nguyen DK, Fleischman RJ, Friedlander S, Zangwill KM. Epidemiology of admissions from the emergency department among febrile infants younger than 90 days in the United States, 2002 to 2012. *Pediatr Emerg Care.* 2020;36:e438-e446.

19. Boddington NL, Pearson I, Whitaker H, Mangtani P, Pebody RG. Effectiveness of influenza vaccination in preventing hospitalization due to influenza in children: A systematic review and meta-analysis. *Clin Infect Dis.* 2021;73:1722-1732.
20. Chaves SS, Perez A, Farley MM, et al. The burden of influenza hospitalizations in infants from 2003 to 2012, United States. *Pediatr Infect Dis J.* 2014;33:912-919.
21. Wang XL, Yang L, Chan KH, et al. Age and sex differences in rates of influenza-associated hospitalizations in Hong Kong. *Am J Epidemiol.* 2015;182:335-344.
22. Mehta K, Morris SK, Bettinger JA, et al. Antiviral use in Canadian children hospitalized for influenza. *Pediatrics.* 2021;148:e2020049672.
23. Ursin RL, Klein SL. Sex differences in respiratory viral pathogenesis and treatments. *Annu Rev Virol.* 2021;8:393-414.
24. Centers for Disease Control and Prevention. Influenza antiviral medications: Summary for clinicians. Available at: https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm (accessed 23 August 2022).
25. Wilkes JJ, Leckerman KH, Coffin SE, et al. Use of antibiotics in children hospitalized with community-acquired, laboratory-confirmed influenza. *J Pediatr*. 2009;154:447–449.
26. Willis GA, Preen DB, Richmond PC, et al; WAIVE Study Team. The impact of influenza infection on young children, their family and the health care system. *Influenza Other Respir Viruses*. 2019;13:18–27.
27. Mattila JM, Vuorinen T, Heikkinen T. Comparative severity of influenza A and B infections in hospitalized children. *Pediatr Infect Dis J.* 2020;39:489-493.
28. Egilmezer E, Walker GJ, Bakthavathsalam P, et al. Systematic review of the impact of point-of-care testing for influenza on the outcomes of patients with acute respiratory tract infection. *Rev Med Virol.* 2018;28:e1995.
29. Hauge SH, Bakken IJ, de Blasio BF, Håberg SE. Risk conditions in children hospitalized with influenza in Norway, 2017-2019. *BMC Infect Dis.* 2020;20:769.

30. Feemster KA, Leckerman KH, Middleton M, et al. Use of administrative data for the identification of laboratory-confirmed influenza infection: The validity of influenza-specific ICD-9 codes. *J Pediatric Infect Dis Soc.* 2013;2:63-66.

Table 1. Demographic and Clinical Characteristics of 703 Children Hospitalized With Influenza.

Characteristic	Age Group						
	<6 mo (n = 137)	6-11 mo (n = 84)	1 yr (n = 116)	2 yr (n = 68)	3-5 yr (n = 101)	6-15 yr (n = 197)	Total (n = 703)
Sex							
Male	74 (54.0)	51 (60.7)	62 (53.4)	42 (61.8)	57 (56.4)	108 (54.8)	394 (56.0)
Female	63 (46.0)	33 (39.3)	54 (46.6)	26 (38.2)	44 (43.6)	89 (45.2)	309 (44.0)
Influenza type							
A	117 (85.4)	67 (79.8)	94 (81.0)	59 (86.8)	79 (78.2)	120 (60.9)	536 (76.2)
B	20 (14.6)	15 (17.9)	20 (17.2)	9 (13.2)	20 (19.8)	75 (38.1)	159 (22.6)
A+B	0	2 (2.4)	2 (1.7)	0	2 (2.0)	2 (1.0)	8 (1.1)
Underlying risk condition	9 (6.6)	15 (17.9)	19 (16.4)	17 (25.0)	39 (38.6)	77 (39.1)	176 (25.0)
Suspected sepsis	57 (41.6)	7 (8.3)	5 (4.3)	6 (8.8)	12 (11.9)	16 (8.1)	103 (14.7)
Antibiotic treatment	75 (54.7)	54 (64.3)	66 (56.9)	40 (58.8)	52 (51.5)	85 (43.1)	372 (52.9)
Intensive care treatment	13 (9.5)	11 (13.1)	14 (12.1)	4 (5.9)	9 (8.9)	23 (11.7)	74 (10.5)
Death	0	0	1 (0.8)	0	0	1 (0.5)	2 (0.3)

Data are n (%).

Table 2. Clinical Features and Management of Hospitalized Children During the Consecutive 5-year Periods Between 1993 and 2018.

Variable	Time Period				
	1993-1998 (n = 138)	1998-2003 (n = 153)	2003-2008 (n = 146)	2008-2013 (n = 114)	2013-2018 (n = 152)
Age at admission (y), median (IQR)	1.3 (0.5-2.8)	2.1 (0.7-6.6)	2.8 (0.8-6.3)	2.7 (0.8-8.3)	3.3 (1.0-9.2)
Duration of hospitalization (d), median (IQR)	2.0 (1.0-4.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)
Duration of hospitalization (d), mean (SD)	3.0 (2.5)	2.5 (2.1)	2.6 (2.9)	2.0 (2.5)	2.3 (2.8)
Intensive care treatment, n (%)	9 (6.5)	20 (13.1)	22 (15.1)	9 (7.9)	14 (9.2)
Suspected sepsis, n (%)	22 (15.9)	31 (20.3)	25 (17.1)	14 (12.3)	11 (7.2)
Antibiotic treatment, n (%)	77 (55.8)	94 (61.4)	78 (53.4)	54 (47.4)	69 (45.4)
Underlying risk condition, n (%)	24 (17.4)	38 (24.8)	40 (27.4)	27 (23.7)	47 (30.9)
Influenza-specific discharge diagnosis, n (%)	85 (61.6)	114 (74.5)	117 (80.1)	95 (83.3)	122 (80.3)

FIGURE LEGENDS

Figure 1.

Numbers of children hospitalized with virologically confirmed influenza A or B during each season of the study.

Figure 2.

Population-based incidence rates of influenza-associated hospitalizations in different age groups of children during the 25-year study period.

Figure 3.

Relative proportions of different age groups of children hospitalized with influenza during the 25-year study period.

LIST OF SUPPLEMENTAL DIGITAL CONTENT

Supplemental Digital Content 1.

Figure that shows the incidence of influenza hospitalizations in boys and girls. tif

Figure 1

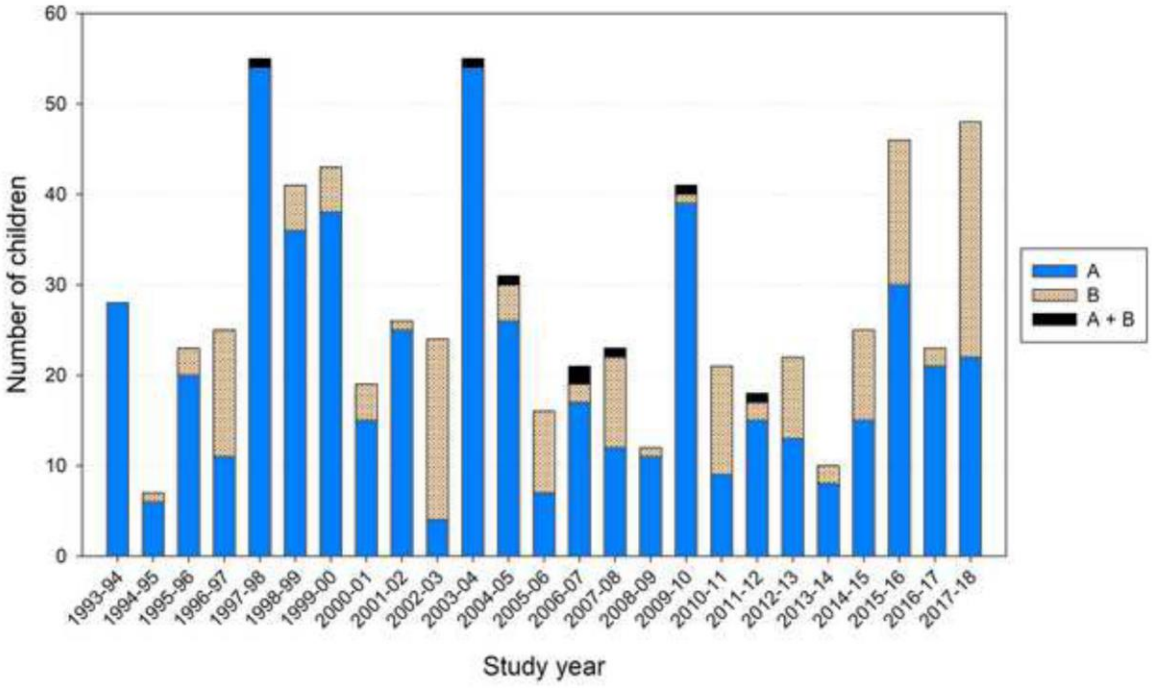

Number of children
60
50
40
30
20
10
0
1993-94
1994-95
1995-96
1996-97
1997-98
1998-99
1999-00
2000-01
2001-02
2002-03
2003-04
2004-05
2005-06
2006-07
2007-08
2008-09
2009-10
2010-11
2011-12
2012-13
2013-14
2014-15
2015-16
2016-17
2017-18
Study year
A
B
A + B

Figure 2

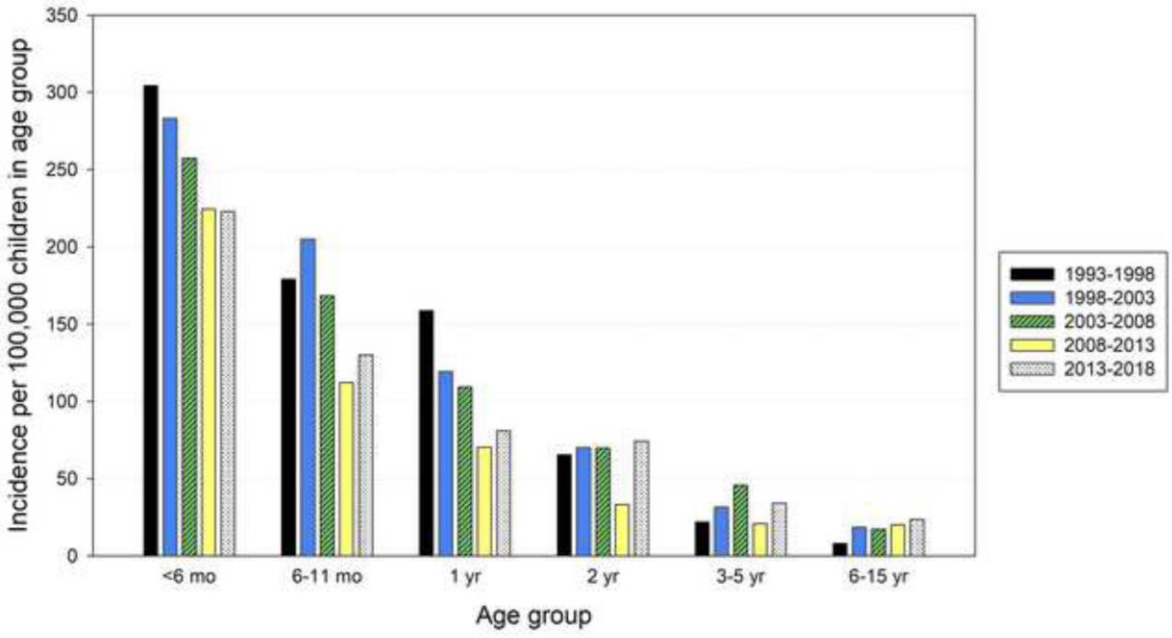
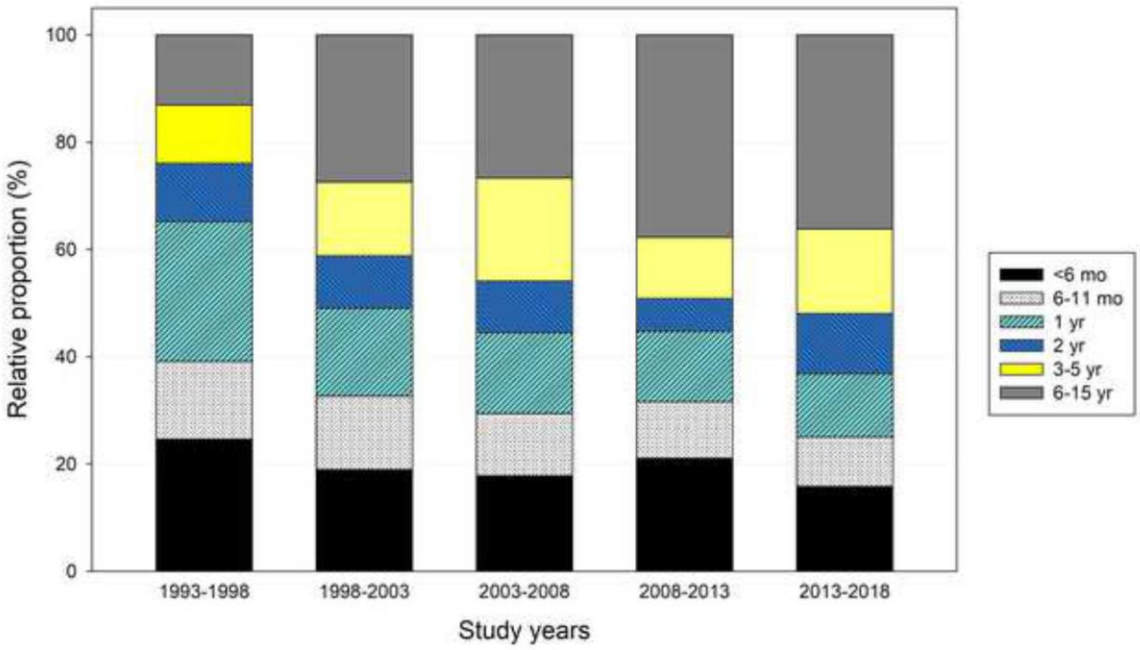

Incidence per 100,000 children in age group
350
300
250
200
150
100
50
0
<6 mo
6-11 mo
1 yr
2 yr
3-5 yr
6-15 yr
Age group
1993-1998
1998-2003
2003-2008
2008-2013
2013-2018

Figure 3


100
80
60
40
20
0
Relative proportion (%)
1993-1998
1998-2003
2003-2008
2008-2013
2013-2018
Study years
<6 mo
6-11 mo
1 yr
2 yr
3-5 yr
6-15 yr

Supplemental Figure

Average annual population-based incidence rates of influenza-associated hospitalizations in boys and girls during the 25-year study period