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Clinical Research

Influenza Vaccination in Patients With Congenital Heart Disease in the Pre-COVID-19 Era: Coverage Rate, Patient Characteristics, and Outcomes

Philip Moons, PhD,[a,b,c] Steffen Fieuws, PhD,[a] Corinne Vandermeulen, MD, PhD,[a] Fouke Ombelet, PhD,[a,d,e] Ruben Willems, PhD,[f] Eva Goossens, PhD,[a,g,h] Liesbet Van Bulck, MSc,[a,h] Michèle de Hosson, MSc,[i] Lieven Annemans, PhD,[f] Werner Budts, MD, PhD,[j,k] Julie De Backer, MD, PhD,[i] Stéphane Moniotte, MD, PhD,[l] Arianne Marelli, MD, MPH,[m] and Katya De Groote, MD, PhD[n] on behalf of the BELCODAC Consortium

[a] *KU Leuven Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium;* [b] *Institute of Health and Care Sciences, University of Gothenburg, Gothenburg, Sweden;* [c] *Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa;* [d] *VIB - Center of Brain and Disease Research, Laboratory of Neurobiology, Leuven, Belgium;* [e] *Department of Neurology, University Hospitals Leuven, Leuven, Belgium;* [f] *Department of Public Health and Primary Care, Ghent University, Ghent, Belgium;* [g] *Faculty of Medicine and Health Sciences, Centre for Research and Innovation in Care, Division of Nursing and Midwifery, University of Antwerp, Antwerp, Belgium;* [h] *Research Foundation Flanders (FWO), Brussels, Belgium;* [i] *Department of Adult Congenital Cardiology, Ghent University Hospital, Ghent, Belgium;* [j] *KU Leuven Department of Cardiovascular Sciences, KU Leuven—University of Leuven, Leuven, Belgium;* [k] *Division of Congenital and Structural Cardiology, University Hospitals Leuven, Leuven, Belgium;* [l] *Division of Pediatric Cardiology, Cliniques Universitaires Saint-Luc (UCLouvain), Brussels, Belgium;* [m] *McGill Adult Unit for Congenital Heart Disease Excellence (MAUDE Unit), McGill University Health Center, Montreal, Quebec, Canada;* [n] *Department of Pediatric Cardiology, Ghent University Hospital, Ghent, Belgium*

ABSTRACT

Background: Influenza vaccination is the most commonly recommended immune prevention strategy. However, data on influenza vaccination in patients with congenital heart disease (CHD) are scarce. In this study, our goals were to: (1) measure vaccination coverage rates (VCRs) for influenza in a large cohort of children, adolescents, and adults with CHD; (2) identify patient characteristics as predictors for vaccination; and (3) investigate the effect of influenza vaccination on hospitalization.

Methods: A nationwide cohort study in Belgium included 16,778 patients, representing 134,782 vaccination years, from the Belgian Congenital Heart Disease Database Combining Administrative and Clinical Data (BELCODAC). Data over 9 vaccination years (2006-2015) were used, and patients were stratified into 5 age cohorts: 6 months

RÉSUMÉ

Contexte : La vaccination contre la grippe est la stratégie de prévention immunitaire la plus couramment recommandée. Cependant, les données sur la vaccination antigrippale chez les patients atteints de cardiopathie congénitale (CC) sont rares. Dans cette étude, nos objectifs étaient de : (1) mesurer les taux de couverture vaccinale (TCV) contre la grippe dans une grande cohorte d'enfants, d'adolescents et d'adultes atteints de CC; (2) identifier les caractéristiques des patients en tant que facteurs prédictifs de vaccination; (3) étudier l'effet de la vaccination contre la grippe sur l'hospitalisation.

Méthodologie : Une étude de cohorte nationale menée en Belgique a regroupé 16 778 patients, représentant 134 782 années de vaccination à partir de la *Belgian Congenital Heart Disease Database Combining Administrative and Clinical Data* (BELCODAC). Des données sur

Influenza vaccination is recommended in cardiac populations because influenza infections are associated with an increase in cardiovascular mortality.[1] Vaccination reduces all-cause mortality, cardiovascular mortality, and major adverse cardiovascular events in people with existing coronary artery disease, and all-cause mortality in heart failure patients.[2] Influenza vaccination is even hypothesized to be preventative toward the development of coronary heart disease.[3,4]

Also patients with congenital heart disease (CHD) ought to receive influenza vaccination as part of comprehensive secondary prevention.[5,6] The coverage of influenza vaccination and its outcome in people with CHD is largely understudied. In a selected group of 123 Canadian adult CHD patients (mean age, 37 years) who participated in a 1-day patient education conference, 68% reported to receive an annual vaccination to protect against the influenza virus.[7] Another Canadian study surveyed all adult patients seen at the CHD outpatient clinic in a 1-year period (n = 124; mean age, 38.4 years).[8] That study showed that 43% of respondents reported undergoing influenza vaccination in the previous season.[8] Adults with CHD were more likely to receive influenza vaccination if they were older, female, and told about the benefits of the vaccine by their physician.[8]

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Corresponding author: Dr Philip Moons, KU Leuven Department of Public Health and Primary Care, Kapucijnenvoer 35, Box 7001, B-3000 Leuven, Belgium. Tel.: +32 16 373315; fax: + 32 16 336970.

E-mail: philip.moons@kuleuven.be

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to 4 years; 5-17 years; 18-49 years; 50-64 years; and 65 years and older.

Results: In the respective age cohorts, the VCR was estimated to be 6.6%, 8.0%, 23.9%, 46.6%, and 72.8%. There was a steep increase in VCRs as of the age of 40 years. Multivariable logistic regression showed that higher anatomical complexity of CHD, older age, presence of genetic syndromes, and previous cardiac interventions were associated with significantly higher VCRs. Among adults, men had lower and pregnant women had higher VCRs. The association between influenza vaccination and all-cause hospitalization was not significant in this study.

Conclusions: The influenza VCR in people with CHD is low, especially in children and adolescents. Older patients, particularly those with complex CHD, are well covered. Our findings should inform vaccination promotion strategies in populations with CHD.

neuf années de vaccination (2006-2015) ont été utilisées et les patients ont été segmentés en cinq cohortes d'âges : 6 mois à 4 ans; 5 à 17 ans; 18 à 49 ans; 50 à 64 ans; et 65 ans et plus.

Résultats : Dans les cohortes d'âges respectives, le TCV a été estimé à 6,6 %, 8,0 %, 23,9 %, 46,6 % et 72,8 %. Une forte augmentation du TCV était perceptible à partir de l'âge de 40 ans. La régression logistique multivariable a montré qu'une complexité anatomique plus grande de la CC, l'âge avancé, la présence de syndromes génétiques et des interventions cardiaques antérieures étaient associés à des TCV significativement plus élevés. Chez les adultes, les hommes avaient un TCV plus faible et les femmes enceintes un TCV plus élevé. L'association entre la vaccination contre la grippe et l'hospitalisation toutes causes confondues n'était pas significative dans cette étude.

Conclusions : Le TCV de la grippe chez les personnes atteintes de CC est faible, en particulier chez les enfants et les adolescents. Les patients plus âgés, notamment ceux atteints de CC complexe, sont bien protégés. Nos résultats devraient éclairer les stratégies de promotion de la vaccination dans les populations atteintes de CC.

With the outbreak of the COVID-19 pandemic, the awareness of the importance of vaccinations against infectious diseases for public and individual's health increased. Previous influenza vaccination status also might also serve as a proxy to inform COVID-19 and target vaccine hesitancy.[9] Therefore, in this study we aimed: (1) to describe the vaccination coverage rate (VCR) for influenza in a large population of children, adolescents, and adults with CHD; (2) to explore patient characteristics as predictors for vaccination; and (3) to investigate the outcome of influenza vaccination in terms of hospitalization.

Methods

Data source

The present study was conducted in Belgium (the setting is described in Supplemental Box S1) using the **Bel**gian **Co**ngenital Heart Disease **D**atabase Combining **A**dministrative and **C**linical Data (BELCODAC).[10] This database comprises data from 18,510 patients with CHD, stemming from 3 Belgian university hospitals. Clinical data from the hospital information system were merged with administrative data on health care use, pharmaceutics, and outcomes. Data from 2006 to 2015 were available. Details on the construction and composition of BELCODAC are described in a methods article.[10] Approval of the ethics committees and regulatory authorities were obtained (details are described in Supplemental Box S2).

Measurements and definitions

The following variables of BELCODAC were used for the present study: sex, birth year, employment status, type of heart defect, complexity of heart defect, previous cardiac intervention, the presence of a genetic syndrome, pregnancy status, household income, and all-cause hospitalizations. In BELCODAC, the different types of heart disease were categorized according to a modified version of the **Con**genital **Cor**vitia (CONCOR) classification, and the categorization of the complexity of the heart defects was on the basis of the Bethesda classification.[10] We defined patient years in terms of vaccination years, starting on September 1 of each year and ending on August 31 of the next year. Hence, the follow-up period in this study ran from September 1, 2006 to August 31, 2015. For the evaluation of outcome, we investigated if vaccination between September 1 and December 31 was associated with reduced hospitalization between January 1 and April 30 of the following year (called outcome observation period).

Vaccines that were delivered by a pharmacist were recorded in BELCODAC. Vaccinations provided to employees by their employer, or administered to residents of nursing homes are not available in BELCODAC. Older people with CHD residing in a nursing home comprise a small proportion of the sample (n = 46), and therefore, will not bias the findings. To account for the missing vaccinations in employees, we adjusted the VCR in BELCODAC by the estimated proportion of employees who received their vaccine at work (see *Statistical Analyses* section). Data on the VCR in the general population are obtained from the Socialistic Mutuality, covering 28.1% of the Belgian population.[11]

Study population

This study yielded a sample of 16,778 patients, representing 134,782 vaccination years. The flow chart of patient selection is given in Figure 1. Overall, 13,098 patients (77.3%) contributed the full 9 years of follow-up. In this sample, 49.3% were men, 49.2% had a heart defect of simple complexity, and 10.4% had a complex heart lesion. The number of patients who contributed to the age cohort of 6 months to 4 years was 5065; 5-17 years was 7801; 18-49 years was 8478; 50-64 years was 1948; and 65 years and older was 726. These numbers are not mutually exclusive because some patients contributed to more than 1 age cohort. The characteristics of patients in the overall sample and the age cohorts are detailed in Table 1.

Statistical analyses

All analyses have been performed using SAS software, version 9.4 of the SAS System for Windows (SAS Institute Inc, Cary, NC). For the descriptive statistics of patient characteristics, absolute numbers and percentages were reported. The percentages for VCR and their 95% confidence intervals (CIs) were calculated using generalized estimating equations (GEE)

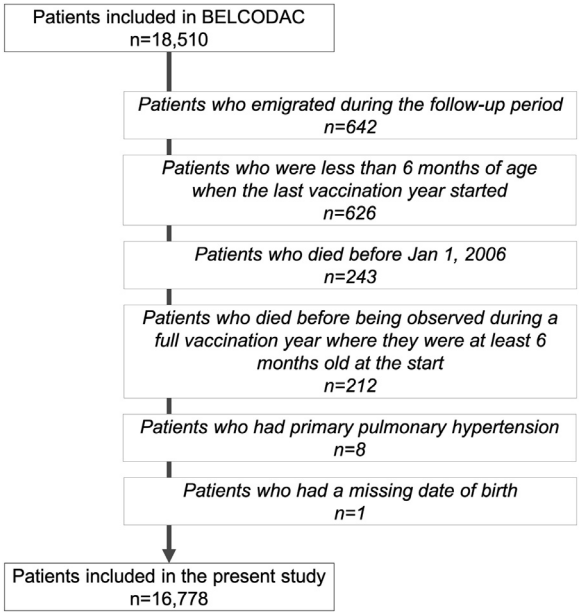

Figure 1. Flow chart of patient selection. BELCODAC, **Bel**gian **Co**ngenital Heart Disease **D**atabase Combining **A**dministrative and **C**linical Data.

with a compound symmetric working correlation matrix.[12] This approach accounts for the clustered structure of the data, resulting from multiple vaccination years per subject. Predictors of vaccination were tested using multivariable logistic regression models with GEE, and expressed as odds ratios and 95% CIs.

To investigate the relationship between vaccination and hospitalization, we used the self-controlled case series method.[13] It is a method in which individuals act as their own control. In such self-matched, within-person comparisons, fixed within-person confounders are implicitly controlled for. Patients in BELCODAC were identified in whom there were 2 consecutive years with 1 year being vaccinated in the period September through December and the other year not at all, or vice versa. The first couple of such consecutive years was used for analysis. However, the influenza seasons 2009-2010 and 2010-2011 were excluded from these analyses, because the influenza epidemic started earlier than usual (Supplemental Fig. S1). A conditional logistic regression model was used to compare the risk for all-cause hospitalization in the outcome period between the year with and the year without vaccination. An adjustment for the ordering of the year of vaccination was made by including a binary variable.

Table 1. Patient characteristics

	Total sample (N = 16,728)	6 months to 4 years (n = 5065)	5-17 years (n = 7801)	18-49 years (n = 8478)	50-64 years (n = 1948)	65 years and older (n = 726)
Male sex	8239 (49.3)	2563 (50.6)	3930 (50.4)	4102 (48.4)	916 (47.0)	308 (42.4)
Being employed*	–	–	–	4701 (56.0)	1137 (59.5)	–
Primary heart defect						
Univentricular physiology	556 (3.3)	228 (4.5)	340 (4.4)	226 (2.7)	14 (0.7)	1 (0.1)
Tetralogy of Fallot	1027 (6.1)	283 (5.6)	467 (6.0)	571 (6.7)	103 (5.3)	15 (2.1)
Double outlet right ventricle	159 (1.0)	54 (1.1)	99 (1.3)	71 (0.8)	6 (0.3)	1 (0.1)
Truncus arteriosus	81 (0.5)	21 (0.4)	60 (0.8)	39 (0.5)	0 (0.0)	0 (0.0)
Transposition of the great arteries	667 (4.0)	285 (5.6)	383 (4.9)	302 (3.6)	4 (0.2)	0 (0.0)
CCTGA	127 (0.8)	28 (0.6)	55 (0.7)	67 (0.8)	18 (0.9)	6 (0.8)
Coarctation of the aorta	1150 (6.9)	372 (7.3)	559 (7.2)	600 (7.1)	97 (5.0)	22 (3.0)
Atrioventricular septal defect	386 (2.3)	143 (2.8)	218 (2.8)	183 (2.2)	13 (0.7)	2 (0.3)
Atrial septal defect type 1	191 (1.1)	46 (0.9)	77 (1.0)	110 (1.3)	25 (1.3)	12 (1.7)
Ebstein malformation	103 (0.6)	28 (0.6)	39 (0.5)	48 (0.6)	21 (1.1)	9 (1.2)
Pulmonary valve abnormality	1570 (9.4)	466 (9.2)	750 (9.6)	865 (10.2)	124 (6.4)	29 (4.0)
Aortic valve abnormality	1192 (7.1)	239 (4.7)	486 (6.2)	769 (9.1)	143 (7.3)	33 (4.6)
Aortic abnormality or LVOTO	680 (4.1)	125 (2.5)	288 (3.7)	444 (5.2)	88 (4.5)	21 (2.9)
Atrial septal defect type 2	2351 (14.1)	634 (12.5)	962 (12.3)	1059 (12.5)	477 (24.5)	278 (38.3)
Ventricular septal defect	3573 (21.4)	1414 (27.9)	1838 (23.6)	1692 (20.0)	190 (9.8)	34 (4.7)
Mitral valve abnormality	713 (4.3)	116 (2.3)	338 (4.3)	443 (5.2)	70 (3.6)	26 (3.6)
Pulmonary vein abnormality	283 (1.7)	71 (1.4)	114 (1.5)	130 (1.5)	61 (3.1)	31 (4.3)
Other	1919 (11.5)	512 (10.1)	728 (9.3)	859 (10.1)	494 (25.4)	206 (28.4)
Complexity of the heart defect						
Simple	8225 (49.2)	2453 (48.4)	3584 (45.9)	4064 (47.9)	1252 (64.3)	497 (68.5)
Moderate	6760 (40.4)	1900 (37.5)	3181 (40.8)	3675 (43.4)	651 (33.4)	221 (30.4)
Complex	1743 (10.4)	712 (14.1)	1036 (13.3)	739 (8.7)	45 (2.3)	8 (1.1)
Genetic syndrome	1459 (8.7)	385 (7.6)	738 (9.5)	838 (9.9)	103 (5.3)	18 (2.5)
Previous cardiac intervention	9362 (56.0)	2421 (47.8)	4204 (53.9)	4651 (54.9)	1309 (67.2)	586 (80.7)
Women with at least 1 pregnancy	–	–	–	1068 (24.4)†	–	–
Minimal household income relative to income status of the population in Flanders‡						
< P25 (€14,990)§	3036 (18.4)	618 (12.7)	1298 (15.5)	1318 (15.6)	248 (12.8)	161 (22.3)
P25-P75 (median = €24,054)‖	7254 (43.9)	1916 (39.4)	2945 (38.1)	3590 (42.6)	802 (41.5)	429 (59.3)
> P75 (€39,006)¶	6223 (37.7)	2331 (47.9)	3384 (46.4)	3527 (41.8)	882 (45.7)	133 (18.4)

Data are presented as n (%). The sample size of the age cohorts is not mutually exclusive because some patients contributed to more than 1 age cohort

CCTGA, congenitally corrected transposition of the great arteries; LVOTO, left ventricular outflow tract obstruction; P25, Percentile 25; P75, Percentile 75; PPP, power purchase parity.

*Employment status in 2011 (denominator for 18-49 years = 8400; for 50-64 years = 1911 because of missing values).

†Only women in the denominator.

‡Household income in Flanders in 2012.

§€14,990 ≈ CAD19,282 ≈ US$ PPP 12,322.

‖€24,054 ≈ CAD 30,941 ≈ US$ PPP 19,772.

¶€39,006 ≈ CAD 50,174 ≈ US$ PPP 32,063.

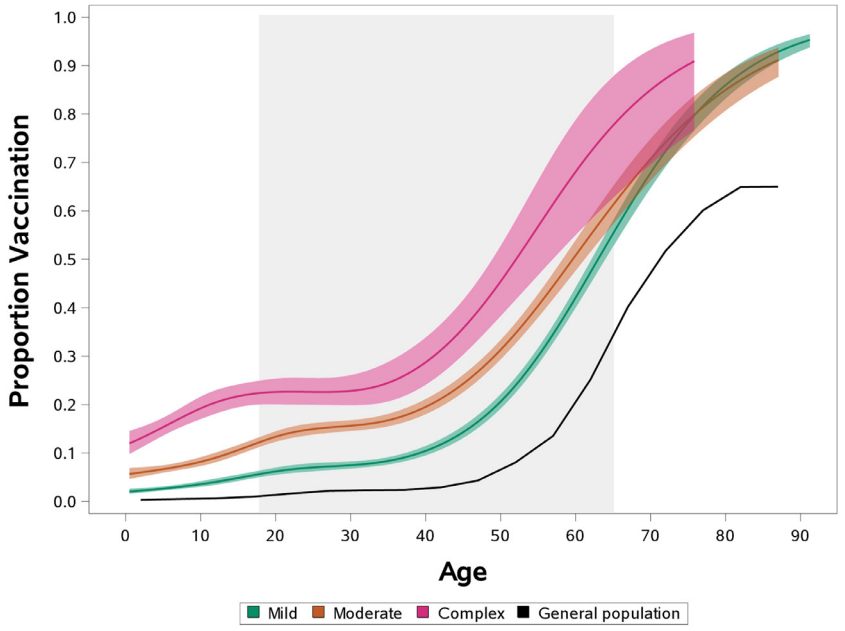

Figure 2. Vaccination coverage rates in patients with simple, moderate, and complex congenital heart disease compared with the general population. Data of the general population are obtained using the Socialistic Mutuality[11]; these data do not include vaccinations at work (professionally active zone indicated in **grey shade**).

Results were reported separately for 5 age cohorts: 6 months to 4 years; 5-17 years; 18-49 years; 50-64 years; and 65 years and older. However, to depict the VCR as a function of age as a continuous variable over the whole age range and compare it with the VCR in the general population restricted cubic splines with 5 knots were used. Because BELCODAC only included vaccines that were delivered by a pharmacist, we needed to supplement our calculations in the 18- to 49-year-old and 50- to 64-year-old cohorts with estimations of the vaccinations obtained at work. From a survey among employed people in Belgium, we could estimate that in the 18- to 49-year-old age cohort, 19.3% of the employed persons were vaccinated at work, whereas this was 23.4% for the 50- to 64-year-old cohort.[14]

Results

VCR

In the different age cohorts, the VCR was estimated to be 6.6% (95% CI, 6.1-7.2), 8.0% (95% CI, 7.5-8.6), 23.9% (95% CI, 22.1-25.8), 46.6% (95% CI, 44.1-49.1), and 72.8% (95% CI, 69.9-75.5), respectively. For the 18-49 years age cohort, the VCR in BELCODAC was 13.1%, which could be supplemented with the 10.8% estimated VCR at work (56.0% of this age cohort with CHD are employed × 19.3% of employees are vaccinated at work[14]). For the 50-64 years age cohort, BELCODAC recorded a VCR of 32.7%, to be supplemented with 13.9% estimated VCR at work (59.5% of this age cohort with CHD are employed × 23.4% of employees are vaccinated at work[14]). The CIs for the VCR do not only take into account the uncertainty of the VCR estimate on the basis of BELCODAC, but also the uncertainty in estimate of the percentage of employees being vaccinated at work.

Figure 2 represents the VCR across the lifespan for people with simple, moderate, and complex heart defects. There was a steep growth in VCR as of the age of 40 years. The pattern over the lifespan followed that of the general population, although the VCRs were higher in those with CHD, with the highest VCR in individuals with complex heart defects.

Patient characteristics and VCR

The VCR differed in subgroups of CHD patients (Table 2). Patients with complex heart defects, genetic syndromes, and previous cardiac interventions had a consistently higher VCR. The highest VCRs were seen in patients with univentricular physiology, double outlet right ventricle, truncus arteriosus, congenitally corrected transposition of the great arteries, and atrioventricular septal defects (Table 2). Data for employed and unemployed adults are reported in Supplemental Table S1.

Multivariable logistic regression models using GEE showed that a higher complexity of the heart defect, a higher age, the presence of a genetic syndrome, and a history of cardiac interventions was associated with significantly higher VCRs (Table 3). Only in the adult age groups, male sex was related to lower VCRs, and pregnant women had a higher VCR. Lower household income did not yield lower VCRs (Table 3). Subanalysis on employed and unemployed adults is reported in Supplemental Table S2 and largely confirmed the overall analyses.

Outcome of influenza vaccination in patients with CHD

All-cause hospitalizations occurred in 12.5%, 5.4%, 6.7%, 10.6%, and 16.8% of the outcome observation periods (January through April) in the different age cohorts, respectively. The self-controlled case series method (n = 2549), with

Table 2. Vaccination coverage rate in the different age cohorts and subgroups

Vaccination status per patient year	6 months to 4 years (n = 5065)	5-17 years (n = 7801)	18-49 years (n = 8478)*	50-64 years (n = 1948)*	65 years and older (n = 726)
Overall	6.6 (6.1-7.2)	8.0 (7.5-8.6)	13.1 (12.5-13.7)	32.7 (30.9-34.5)	72.8 (69.9-75.5)
Sex					
Male	7.3 (6.5-8.1)	8.8 (8.1-9.6)	12.0 (11.2-12.9)	29.1 (26.7-31.8)	71.8 (67.2-76.1)
Female	5.9 (5.2-6.7)	7.2 (6.6-8.0)	14.1 (13.3-15.0)	35.8 (33.2-38.4)	73.6 (69.8-77.0)
Primary heart defect					
Univentricular physiology	28.2 (23.6-33.4)	32.3 (28.2-36.7)	30.8 (26.1-36.0)	54.8 (33.5-74.5)	100.0 (–)
Tetralogy of Fallot	13.0 (10.1-16.5)	13.8 (11.3-16.7)	21.7 (19.0-24.8)	46.6 (37.9-55.5)	79.4 (59.1-91.2)
Double outlet right ventricle	20.4 (13.1-30.5)	20.2 (14.1-28.3)	28.8 (20.8-38.3)	54.2 (22.2-83.1)	100.0 (–)
Truncus arteriosus	14.1 (7.2-25.9)	23.3 (15.5-33.6)	39.6 (27.5-53.2)	–	–
Transposition of the great arteries	6.8 (4.8-9.5)	8.6 (6.5-11.3)	12.3 (9.6-15.6)	53.1 (15.3-87.7)	–
CCTGA	13.2 (5.4-28.8)	21.1 (13.2-32.0)	17.4 (11.1-26.1)	57.7 (36.3-76.6)	92.8 (67.3-98.8)
Coarctation of the aorta	6.9 (5.1-9.3)	8.5 (6.8-10.7)	11.5 (9.6-13.7)	33.5 (25.9-42.1)	61.4 (43.4-76.8)
Atrioventricular septal defect	15.4 (11.0-21.1)	24.4 (19.6-29.8)	43.9 (37.4-50.5)	73.1 (45.9-89.7)	100.0 (-)
Atrial septal defect type 1	9.2 (4.0-20.0)	15.7 (9.7-24.5)	23.2 (16.9-30.9)	55.5 (38.1-71.7)	64.1 (38.5-83.6)
Ebstein malformation	7.7 (2.7-19.8)	11.7 (5.5-22.9)	13.4 (7.2-23.4)	45.7 (28.1-64.4)	91.0 (65.7-98.2)
Pulmonary valve abnormality	2.6 (1.7-4.1)	3.7 (2.8-4.9)	9.9 (8.3-11.7)	27.8 (21.6-35.1)	82.2 (67.0-91.3)
Aortic valve abnormality	8.0 (5.4-11.5)	9.1 (7.1-11.6)	17.5 (15.3-19.9)	42.5 (35.5-49.7)	69.7 (55.1-81.3)
Aortic abnormality or LVOTO	4.1 (2.1-7.8)	6.3 (4.3-9.0)	13.3 (10.9-16.2)	29.0 (21.7-37.6)	63.9 (43.3-80.4)
Atrial septal defect type 2	4.8 (3.6-6.2)	5.1 (4.0-6.5)	11.0 (9.5-12.6)	34.2 (30.6-38.0)	76.4 (72.0-80.4)
Ventricular septal defect	2.8 (2.2-3.6)	2.9 (2.3-3.6)	7.4 (6.4-8.5)	22.5 (17.7-28.2)	62.7 (47.9-75.5)
Mitral valve abnormality	5.7 (3.0-10.4)	6.8 (5.0-9.2)	10.5 (8.5-13.0)	32.9 (23.5-43.9)	65.1 (47.6-79.4)
Pulmonary vein abnormality	10.6 (6.1-17.9)	5.6 (3.0-10.2)	8.2 (5.3-12.6)	31.7 (23.0-41.9)	77.8 (60.5-89.0)
Other	4.3 (3.1-6.0)	4.5 (3.3-5.9)	8.5 (7.1-10.1)	26.3 (23.2-29.7)	68.8 (63.0-74.1)
Complexity of the heart defect					
Simple	3.0 (2.5-3.6)	3.6 (3.1-4.2)	9.2 (8.5-10.0)	28.9 (26.8-31.2)	73.0 (69.6-76.2)
Moderate	7.9 (7.0-9.0)	9.2 (8.4-10.1)	15.6 (14.7-16.7)	38.2 (34.9-41.5)	71.6 (66.0-76.6)
Complex	15.4 (13.3-17.8)	19.5 (17.5-21.7)	21.9 (19.5-24.5)	57.6 (44.2-70.0)	94.3 (72.1-99.1)
Genetic syndrome					
No	6.0 (5.4-6.6)	7.0 (6.5-7.5)	11.1 (10.5-11.7)	31.8 (30.0-33.7)	72.6 (69.7-75.4)
Yes	14.3 (11.7-17.4)	18.2 (15.9-20.8)	31.3 (28.6-34.2)	47.7 (39.0-56.5)	81.9 (61.4-92.8)
Previous cardiac interventions					
No	2.7 (2.3-3.2)	3.7 (3.3-4.3)	9.8 (9.1-10.6)	25.1 (22.6-27.7)	67.0 (61.5-72.1)
Yes	11.5 (10.4-12.6)	11.8 (11.0-12.7)	15.9 (15.0-16.8)	36.8 (34.5-39.1)	75.0 (71.8-77.9)
Pregnant women					
No	–	–	12.9 (12.3-13.6)	–	–
Yes	–	–	11.4 (10.0-12.9)	–	–
Household income					
< P25 (€14,990)†	5.7 (4.3-7.5)	7.3 (6.1-8.8)	15.9 (14.2-17.7)	42.0 (36.5-47.7)	76.1 (69.8-81.5)
P25-P75 (median = €24,054)‡	7.3 (6.4-8.3)	8.4 (7.6-9.2)	13.5 (12.7-14.4)	40.5 (37.7-43.4)	74.2 (70.8-77.3)
> P75 (€39,006)§	6.7 (6.0-7.5)	8.1 (7.5-8.8)	11.7 (11.0-2.3)	27.1 (25.1-29.2)	67.8 (62.3-72.8)

Data are presented as percentages on the basis of generalized estimating equations (95% confidence interval).

BELCODAC, **Bel**gian **Co**ngenital Heart Disease **D**atabase Combining **A**dministrative and **C**linical Data; CCTGA, congenitally corrected transposition of the great arteries; CHD, congenital heart disease; LVOTO, left ventricular outflow tract obstruction; P25, Percentile 25; P75, Percentile 75; PPP, power purchase parity; VCR, vaccination coverage rate.

*Data obtained in BELCODAC, which has to be supplemented by the estimated VCR at work for CHD (10.8% for people aged 18-49 years; 13.9% for people aged 50-64 years).

†€14,990 ≈ CAD19,282 ≈ US$ PPP 12,322.

‡€24,054 ≈ CAD 30,941 ≈ US$ PPP 19,772.

§€39,006 ≈ CAD 50,174 ≈ US$ PPP 32,063.

correction for the ordering of the year of vaccination, did not yield a statistically significant association between vaccination and all-cause hospitalization (Table 4). Observably, the odds ratios were the lowest in the age cohorts that are most susceptible for infection-related diseases, being children and elderly individuals.

Discussion

To our knowledge, this is the first large-scale study on vaccination rates for influenza in children, adolescents, and adults with CHD. We found that: (1) the VCR was very low in children and adolescents, and increased substantially as of the age of 40 years; (2) that the VCR was associated with higher anatomical complexity of CHD, older age, presence of genetic syndromes, previous cardiac interventions, female sex, and pregnancy; and (3) we could not confirm a statistical association between vaccination and all-cause hospitalizations.

In people with CHD, the VCR was higher than in the general population,[11] in children,[15] and adults with other chronic medical conditions,[16] and in older persons in Belgium.[17] However, the estimated VCR in pregnant women with CHD was lower than in the general population of pregnant woman in Belgium.[18] Compared with previous studies in adults with CHD, which were conducted in Canada,[7,8] the VCR in our adult cohort was lower. This can be explained by the fact that the present study did not rely on self-report, which is likely to over-report the true VCRs,[19] and because universal influenza vaccination is recommended and publicly funded for all individuals as of the age of 6 months in the absence of

Table 3. Patient characteristics as predictors for vaccination

	6 months to 4 years	5-17 years	18-49 years	50-64 years	65 years and older
Sex					
Male	1.004 (0.993-1.016)	1.007 (0.997-1.018)	0.980 (0.968-0.991)	0.941 (0.909-0.974)	0.995 (0.940-1.053)
Female	Reference	Reference	Reference	Reference	Reference
Complexity of the heart defect					
Simple	Reference	Reference	Reference	Reference	Reference
Moderate	1.021 (1.008-1.034)	1.026 (1.016-1.037)	1.035 (1.021-1.048)	1.073 (1.032-1.116)	0.987 (0.926-1.051)
Complex	1.116 (1.083-1.150)	1.172 (1.141-1.205)	1.157 (1.121-1.193)	1.335 (1.178-1.513)	1.304 (1.187-1.434)
Age at start of influenza season	1.005 (1.002-1.008)	1.003 (1.002-1.004)	1.004 (1.004-1.005)	1.023 (1.019-1.026)	1.009 (1.005-1.014)
Presence of a genetic syndrome	1.084 (1.050-1.118)	1.117 (1.090-1.144)	1.248 (1.212-1.285)	1.266 (1.153-1.390)	1.229 (1.024-1.475)
Cardiac intervention before influenza season	1.053 (1.040-1.066)	1.044 (1.032-1.055)	1.056 (1.043-1.068)	1.129 (1.092-1.168)	1.110 (1.049-1.174)
Pregnancy	–	–	1.052 (1.038-1.067)	–	–
Household income, log2	1.002 (0.998-1.007)	1.003 (1.000-1.006)	0.996 (0.993-1.000)	0.976 (0.965-0.986)	0.967 (0.944-0.990)

Data are presented as odds ratio (95% confidence interval) on the basis of multivariable logistic regression using generalized estimating equations, and adjusted for centre.

Table 4. Association of vaccination with hospitalization using self-controlled case series method

	6 months to 4 years (n = 328)	5-17 years (n = 509)	18-49 years (n = 1192)	50-64 years (n = 392)	65 years and older (n = 128)
Vaccination as predictor of hospitalization	0.752 (0.504-1.120)	0.958 (0.636-1.441)	1.265 (0.949-1.687)	0.810 (0.447-1.467)	0.768 (0.397-1.486)

Data are presented as odds ratio (95% confidence interval) on the basis of the self-controlled case series method[13] with correction for the ordering of the year of vaccination.

contraindications in the regions where these previous studies have been performed.[20]

It could be argued that the VCR in children with CHD should be higher. Indeed, children with heart diseases aged 0-4 years have a 6.2 greater odds, and those aged 5-9 years have a 30.6 greater odds of being hospitalized for influenza.[21] When admitted to the hospital for influenza, such children are at significantly increased risk for in-hospital mortality, acute respiratory failure, acute kidney injury, need for invasive and noninvasive mechanical ventilation, myocarditis, and need for extracorporeal membrane oxygenation.[22] Understandably, this corresponded with a higher length of stay.[22] These complications were found to be independent of the severity of the CHD, indicating that children and adolescents with mild or moderate heart defects also benefit from vaccination.[22]

The predictors for vaccination were the complexity of the heart defect, an older age, genetic syndromes, and a history of cardiac interventions. In the adult age cohort, female sex and pregnancy was also predictive. Our findings were in line with a previous study in adults with CHD, indicating that influenza vaccination was more prevalent in older and female patients.[8] The household income did not play a significant role. This suggest that the (modest) co-pay is not a barrier in getting vaccinated. Awareness in the population and among health care providers is probably a more important driver. Education programs and public awareness campaigns might further increase the VCR, especially in people with moderate or simple heart defects.

In contrast with prospective effectiveness studies, we were not able to show a significant effect of vaccination on all-cause hospitalizations. It is likely that this lack of significant associations had methodological reasons. As an outcome, we could only investigate all-cause hospitalization because we did not have data on infection-related hospitalizations, which obviously would be more sensitive. Further, the number of patients in the different age cohorts included in the self-controlled case series is relatively small. This was particularly the case in children and elderly persons, who are most susceptible for infection-related diseases. Knowing that the number needed to vaccinate to prevent 1 hospitalization in elderly persons is 777,[23] our outcome analysis does not have sufficient power.

Methodological considerations

The present study has several strengths. The study was performed on BELCODAC, which contains data on a large population of patients with CHD over the entire age spectrum.[10] Vaccination rates could be derived from administrative data on the provision of vaccines by pharmacists, and therefore, we did not have to rely on self-report. BELCODAC comprises data over a period of 10 years. This allowed us to investigate 9 consecutive influenza seasons. To account for clustering of data, we used GEE.

However, there were some methodological limitations that we need to consider in the interpretation of the findings. First, BELCODAC has a slight over-representation of complex CHD in the age cohorts of children and adolescents, which might have resulted in a slight overestimation of the VCR in these young age groups. Second, vaccinations obtained at work were not recorded in BELCODAC. Hence, we needed to estimate the VCR among employees, to adjust the VCR in CHD patients. Obviously, this estimation is on the basis of the assumption that the employed CHD population behaves identically to other employees. However, it is the best estimate that can be made. Third, we were not able to assess the different types of heart defect as predictors of

VCR in multivariable models. Although the overall sample in BELCODAC is large, specific subgroups of heart defects comprise too few patients. Fourth, when estimating the VCR in pregnant women, we included all women who have had health care encounters for prenatal or postnatal follow-up and counselling, or giving birth, in each influenza season. Doing so, we might have slightly overestimated the denominator. Fifth, we used a self-controlled case series design to evaluate the relationship between vaccination and hospitalization.[13] Although this design has been used in previous vaccination studies, violation of assumptions cannot be completely excluded. For instance, it is possible that being hospitalized in one year would increase the wish for vaccination the next year, or that an infection in a nonvaccinated year would result in mortality and thus drop-out of the analysis. In the present study, we adjusted the analysis for order of vaccination (yes-no or no-yes). The order did not significantly explain the findings. Sixth, BELCODAC does not comprise data on the physiological staging of the newly developed Adult Congenital Heart Disease Anatomic and Physiological (ACHD AP) classification.[24] Because this new classification has superior prognostic power,[25] it could also be a predictor for VCR and it could moderate the effect of vaccination on outcomes. Finally, our study was not designed to investigate nonmedical factors that affect VCR rates and might account for vaccine hesitancy but such factors merit to be explored in future studies.[9]

Conclusions

In our study, the VCR for influenza was very low in children and adolescents with CHD. The VCR with increased as of the age of 40 years. Higher complexity of CHD, older age, presence of genetic syndromes, and previous cardiac interventions were associated with significantly higher VCRs. The VCR in those with CHD was higher than in the general population or in people with other chronic medical conditions in Belgium. In the context of the global COVID-19 pandemic, our study establishes baseline rates of vaccination for the most commonly recommended preventive immune therapy across the lifespan. Nonmedical factors driving vaccine hesitancy need to be explored in future studies to ensure comprehensive vaccination campaign strategies in vulnerable populations such as those with CHD.

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Disclosures

The authors have no conflicts of interest to disclose.

References

1. Nguyen JL, Yang W, Ito K, et al. Seasonal influenza infections and cardiovascular disease mortality. JAMA Cardiol 2016;1:274–81.
2. Rodrigues BS, Alves M, Duarte GS, et al. The impact of influenza vaccination in patients with cardiovascular disease: an overview of systematic reviews. Trends Cardiovasc Med 2021;31:315–20.
3. Aidoud A, Marlet J, Angoulvant D, et al. Influenza vaccination as a novel means of preventing coronary heart disease: effectiveness in older adults. Vaccine 2020;38:4944–55.
4. Muscente F, De Caterina R. Causal relationship between influenza infection and risk of acute myocardial infarction: pathophysiological hypothesis and clinical implications. Eur Heart J Suppl 2020;22: E68–72.
5. Grohskopf LA, Alyanak E, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices - United States, 2019-20 influenza season. MMWR Recomm Rep 2019;68:1–21.
6. Buchy P, Badur S. Who and when to vaccinate against influenza. Int J Infect Dis 2020;93:375–87.
7. Harrison JL, Silversides CK, Oechslin EN, Kovacs AH. Healthcare needs of adults with congenital heart disease: study of the patient perspective. J Cardiovasc Nurs 2011;26:497–503.
8. Bare I, Crawford J, Pon K, Farida N, Dehghani P. Frequency and consequences of influenza vaccination in adults with congenital heart disease. Am. J. Cardiol. 2018;121:491–4.
9. Larson HJ, Jarrett C, Schulz WS, et al. Measuring vaccine hesitancy: the development of a survey tool. Vaccine 2015;33:4165–75.
10. Ombelet F, Goossens E, Willems R, et al. Creating the BELgian COngenital heart disease database combining administrative and clinical data (BELCODAC): rationale, design and methodology. Int J Cardiol 2020;316:72–8.
11. Risicogroepen griepvaccinatie te weinig bereikt met circuit arts-apotheker. [Risk groups for influenza vaccination are not well reached by the circle of physicians and pharmacists]. Brussels: Socialistische Mutualiteiten; 2020 [in Dutch].
12. Molenberghs G, Verbeke G. Models for discrete longitudinal data. New York: Springer-Verlag; 2005.
13. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ 2016;354: i4515.
14. Indiville. Onderzoek griepvaccinatie bij werknemers. [Study on influenza vaccination in employees]. Brussels: Mensura; 2020 [in Dutch].
15. Goeyvaerts N, Willem L, Van Kerckhove K, et al. Estimating dynamic transmission model parameters for seasonal influenza by fitting to age and season-specific influenza-like illness incidence. Epidemics 2015;13:1–9.

16. Boey L, Bosmans E, Ferreira LB, et al. Vaccination coverage of recommended vaccines and determinants of vaccination in at-risk groups. Hum Vaccin Immunother 2020;16:2136–43.

17. Devos C, Cordon A, Lefèvre M, et al. De performantie van het Belgische gezondheidssysteem – Rapport 2019. [The performance of the Belgian healthcare system - Report 2019]. Brussels: Belgian Health Care Knowledge Centre (KCE); 2019 [in Dutch].

18. Maertens K, Braeckman T, Blaizot S, et al. Coverage of recommended vaccines during pregnancy in Flanders, Belgium. Fairly good but can we do better? Vaccine 2018;36:2687–93.

19. Rolnick SJ, Parker ED, Nordin JD, et al. Self-report compared to electronic medical record across eight adult vaccines: do results vary by demographic factors? Vaccine 2013;31:3928–35.

20. Andrew MK, McNeil SA. Influenza vaccination and the evolution of evidence-based recommendations for older adults: a Canadian perspective. Vaccine 2021;39(suppl 1):A36–41.

21. Hauge SH, Bakken IJ, de Blasio BF, Haberg SE. Risk conditions in children hospitalized with influenza in Norway, 2017-2019. BMC Infect Dis 2020;20:769.

22. Ghimire LV, Chou FS, Moon-Grady AJ. Impact of congenital heart disease on outcomes among pediatric patients hospitalized for influenza infection. BMC Pediatr 2020;20:450.

23. Kelly H, Attia J, Andrews R, Heller RF. The number needed to vaccinate (NNV) and population extensions of the NNV: comparison of influenza and pneumococcal vaccine programmes for people aged 65 years and over. Vaccine 2004;22:2192–8.

24. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e81–192.

25. Ombelet F, Goossens E, Van De Bruaene A, Budts W, Moons P. Newly developed adult congenital heart disease anatomic and physiological classification: first predictive validity evaluation. J Am Heart Assoc 2020;9:e014988.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at doi:10.1016/j.cjca.2021.04.010.