Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 72 / No. 27
July 7, 2023

Inpatient Hospitalization Costs Associated with Birth Defects Among Persons Aged <65 Years — United States, 2019

Justin Swanson, MPH[1]; Elizabeth C. Ailes, PhD[2]; Janet D. Cragan, MD[2]; Scott D. Grosse, PhD[3]; Jean Paul Tanner, PhD[1]; Russell S. Kirby, PhD[1]; Norman J. Waitzman, PhD[4]; Jennita Reefhuis, PhD[2]; Jason L. Salemi, PhD[1]

Abstract

Changing treatments and medical costs necessitate updates to hospitalization cost estimates for birth defects. The 2019 National Inpatient Sample was used to estimate the service delivery costs of hospitalizations among patients aged <65 years for whom one or more birth defects were documented as discharge diagnoses. In 2019, the estimated cost of these birth defect–associated hospitalizations in the United States was $22.2 billion. Birth defect–associated hospitalizations bore disproportionately high costs, constituting 4.1% of all hospitalizations among persons aged <65 years and 7.7% of related inpatient medical costs. Updating estimates of hospitalization costs provides information about health care resource use associated with birth defects and the financial impact of birth defects across the life span and illustrates the need to determine the continued health care needs of persons born with birth defects to ensure optimal health for all.

Introduction

In the United States, major structural birth defects attributable to genetic, chromosomal, teratogenic, or unknown etiologies affect approximately 3% of live births (*1*) and are the leading cause of infant mortality, responsible for 21% of newborn and infant deaths (*2*). Their treatments incur significant financial costs throughout a person's lifetime. As treatments and medical costs change, updates to hospitalization cost estimates for birth defects are needed.

Methods

Developed for the Healthcare Cost and Utilization Project (HCUP), the National Inpatient Sample (NIS) is the largest publicly available, all-payor inpatient care database in the United States.* NIS uses a 20% systematic sampling of all discharges from short-term, nonfederal community hospitals. Because NIS does not identify patients across multiple hospital visits, the unit of analysis for this study is individual hospitalization rather than individual patient. To reduce the impact of potential miscoding of age-related abnormalities as birth defects (particularly cardiovascular defects) (*3*), only patients aged <65 years discharged during January 1–December 31, 2019 were included. Birth hospitalizations were determined separately from other hospitalizations during the first year of life to better differentiate the costs of birth defects from routine delivery costs. Records missing values of age or billed charges were excluded. Sampling weights for the remaining hospitalizations were adjusted to retain total hospitalization frequency and cost.

Cost estimates were calculated as the product of the amount billed for a hospitalization and the corresponding hospital-level cost-to-charge ratios. HCUP-provided cost-to-charge ratios are computed on an annual basis for each hospital (total institutional service delivery costs divided by total amount charged by

* https://www.hcup-us.ahrq.gov/db/nation/nis/NISIntroduction2019.pdf

INSIDE

Continuing Education examination available at https://www.cdc.gov/mmwr/mmwr_continuingEducation.html

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

the hospital).[†] NIS records facility charges but not professional fees charged by physicians who are not hospital employees.

Birth defects were identified by scanning up to 40 available diagnosis code fields associated with each hospitalization among codes Q00–Q99 (congenital malformations, deformations, and chromosomal abnormalities) of the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM). Patent ductus arteriosus (Q25.0) and atrial septal defect (Q21.1) were not considered birth defects when occurring in neonates aged <28 days or with an associated indicator of preterm birth (P07.2 or P07.3). In addition, 23 conditions classified within the Q00–Q99 code range that are commonly considered benign or are otherwise unlikely to contribute to hospitalization costs were not considered birth defects for the purposes of this analysis (Supplementary Table, https://stacks.cdc.gov/view/cdc/130207).

Sampling weights were applied to calculate national estimates of hospitalization frequency and cost. Mean, median, and total costs were calculated by patient demographic and birth defect code characteristics. Mean hospitalization costs were stratified by age group for selected individual birth defects and birth defect categories. If a hospitalization was associated with more than one defect included in the table, the full cost of the hospitalization was included for each defect. The individual birth defects listed include those defined in the National Birth Defects Prevention Network Congenital Malformations Surveillance Report.[§] Statistical analyses were performed using SAS software (version 9.4; SAS Institute) with survey procedures incorporating sampling design. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.[¶]

Results

During 2019, a total of 937,295 birth defect–associated hospitalizations incurred a total cost of $22,204,754,855 (Table 1), representing 4.1% of hospitalizations and 7.7% of hospitalization costs among persons in the United States aged <65 years. A birth defect code was the principal diagnosis code for 15.8% of all birth defect–associated hospitalizations that were not birth hospitalizations.

Nonbirth hospitalizations of persons aged <1 year at admission were associated with the highest mean ($61,881) and median ($15,708) costs per hospitalization among all age groups (Table 1). Among birth defect–associated hospitalizations during the first year of life, a co-occurring preterm birth diagnosis code was present in 15.3% of hospitalizations, and hospitalizations with a preterm birth diagnosis code were associated with 45.9% of hospitalization costs.

[†] https://www.hcup-us.ahrq.gov/reports/methods/MS2021-05-CCR-Methodologies.pdf

[§] https://www.nbdpn.org/docs/Birth_Defects_Data_and_Directory_2022.pdf

[¶] 45 C.F.R. part 46; 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d), 5 U.S.C. Sect. 552a, 44 U.S.C. Sect. 3501 et seq.

The *MMWR* series of publications is published by the Office of Science, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30329-4027.

Suggested citation: [Author names; first three, then et al., if more than six.] [Report title]. MMWR Morb Mortal Wkly Rep 2023;72:[inclusive page numbers].

TABLE 1. Weighted national estimates of frequencies and costs of hospitalizations with at least one birth defect–associated discharge diagnosis* among persons aged <65 years, by selected characteristics — National Inpatient Sample, United States, 2019

Characteristic	No. of discharges (%)	Total cost, USD (%)	Mean cost, USD	Median cost, USD
All hospitalizations with a birth defect diagnosis	**937,295 (100.0)**	**22,204,754,855 (100.0)**	**23,690**	**7,054**
Position of birth defect diagnosis code, excluding birth hospitalizations (N = 583,665)				
Principal diagnosis	92,200 (15.8)	**4,628,169,299 (26.7)**	50,197	21,837
Not principal diagnosis	491,465 (84.2)	**12,734,760,311 (73.3)**	25,912	10,693
Age group at admission, yrs				
Birth	353,630 (37.7)	**4,841,825,245 (21.8)**	13,692	1,668
<1, nonbirth	97,085 (10.4)	**6,007,670,516 (27.1)**	61,881	15,708
1–5	70,405 (7.5)	**2,010,690,220 (9.1)**	28,559	11,495
6–18	84,330 (9.0)	**2,406,631,722 (10.8)**	28,538	13,745
19–64	331,845 (35.4)	**6,937,937,152 (31.2)**	20,907	11,050
Co-occurring preterm birth diagnosis code, first year of life only (N = 450,715)				
Yes	69,145 (15.3)	**4,982,419,450 (45.9)**	72,058	23,567
No	381,570 (84.7)	**5,867,076,311 (54.1)**	15,376	1,865
Primary payer				
Medicare/Medicaid	489,435 (52.2)	**11,830,918,831 (53.3)**	24,173	7,228
Private insurance	377,260 (40.2)	**8,624,077,051 (38.8)**	22,860	6,892
Self-pay/No charge	38,420 (4.1)	**589,451,660 (2.7)**	15,342	4,454
Other	30,810 (3.3)	**1,131,579,789 (5.1)**	36,728	10,309
Missing	1,370 (0.1)	**28,727,525 (0.1)**	20,969	8,138
Race or ethnicity				
Black or African American, non-Hispanic	155,790 (16.6)	**3,643,653,444 (16.4)**	23,388	5,453
White, non-Hispanic	465,705 (49.7)	**10,623,669,704 (47.8)**	22,812	8,254
Hispanic or Latino, all races	159,090 (17.0)	**4,176,577,475 (18.8)**	22,752	6,770
Other race, non-Hispanic	99,905 (10.7)	**2,468,402,379 (11.1)**	26,253	5,128
Missing	56,805 (6.1)	**1,292,451,853 (5.8)**	24,707	3,550
Birth defects category†				
Cardiovascular	209,045 (22.3)	**9,833,000,308 (44.3)**	47,038	15,750
Cardiovascular, critical	32,380 (3.5)	**2,810,676,170 (12.7)**	86,803	29,430
Central nervous system	97,810 (10.4)	**3,170,662,573 (14.3)**	32,417	11,920
Chromosomal	81,450 (8.7)	**2,629,174,588 (11.8)**	32,280	10,393
Cleft lip or palate or both	13,450 (1.4)	**371,907,278 (1.7)**	27,651	9,457
Ear	16,505 (1.8)	**311,185,562 (1.4)**	18,854	1,979
Eye	7,020 (0.7)	**353,579,767 (1.6)**	50,367	13,268
Gastrointestinal	58,630 (6.3)	**2,372,323,342 (10.7)**	40,463	12,043
Genitourinary	190,550 (20.3)	**3,827,722,973 (17.2)**	20,088	5,702
Integumentary	185,165 (19.7)	**1,968,999,140 (8.9)**	10,634	1,587
Musculoskeletal	152,150 (16.2)	**4,139,059,463 (18.6)**	27,204	8,948
Other syndrome affecting multiple systems	29,050 (3.1)	**1,040,175,603 (4.7)**	35,806	12,161
Other defect	42,875 (4.6)	**2,757,425,472 (12.4)**	64,313	11,987

Abbreviations: ICD-10-CM = *International Classification of Diseases, Tenth Revision, Clinical Modification*; USD = U.S. dollars.

* Identified by scanning up to 40 available fields for ICD-10-CM diagnosis codes Q00–Q99: congenital malformations, deformations, and chromosomal abnormalities. Patent ductus arteriosus (Q25.0) and atrial septal defect (Q21.1) were not considered birth defects when occurring in neonates aged <28 days or with an associated indicator of preterm birth (ICD-10-CM codes P07.2 or P07.3). An additional 23 conditions of lesser clinical importance classified within the Q00–Q99 code range were not considered birth defects.

† Birth defects categories correspond to blocks of ICD-10-CM diagnosis codes: cardiovascular (Q20–Q28), central nervous system (Q00–Q07), chromosomal (Q90–Q99), cleft lip/palate (Q35–Q37), ear (Q16–Q17), eye (Q10–Q15), gastrointestinal (Q38–Q45), genitourinary (Q50–Q64), integumentary (Q80–Q85), musculoskeletal (Q65–Q79), and other syndrome (Q87). "Other defect" includes birth defects of the face and neck (Q18), respiratory system (Q30–Q34), and other congenital malformations (Q86 and Q89). Critical cardiovascular defects (https://www.cdc.gov/ncbddd/heartdefects/facts.html) were operationalized using the National Birth Defects Prevention Network Congenital Malformations Surveillance Report (https://www.nbdpn.org/docs/Birth_Defects_Data_and_Directory_2022.pdf). The specific defects included are only those defined in the National Birth Defects Prevention Network Congenital Malformations Surveillance Report; birth defects not included contribute to frequencies and costs aggregated by birth defect category and overall. Because a single hospitalization might include more than one specific birth defect, individual birth defect frequencies might sum to >100% of birth defects categories or overall frequencies, and mean costs multiplied by frequencies will correspondingly sum to >100% of total costs.

The most prevalent birth defect category was cardiovascular defects (22.3%), which were associated with a total cost of $9,833,000,308 (44.3% of all birth defect–associated hospitalization costs) (Table 1). Critical cardiovascular defects alone accounted for 12.7% of birth defect–associated hospitalization costs and had the highest median cost ($29,430) per hospitalization. Among nonbirth hospitalizations of neonates and infants, defects with a mean cost >$150,000 included esophageal atresia ($214,651), interrupted aortic arch ($199,973), and diaphragmatic hernia ($195,456) (Table 2). Although mean costs per nonbirth hospitalization were highest for patients aged <1 year, this was not consistent across individual birth defects

TABLE 2. Weighted national estimates of frequencies and mean costs of birth defect–associated hospitalizations* among persons aged <65 years, by selected specific birth defect and age group — National Inpatient Sample, United States, 2019

	Age group at admission, yrs											
	Birth hospitalization		<1, nonbirth		1–5		6–18		19–64		All age groups	
Birth defect†	No.§	Mean cost, USD	No.§	Mean cost, USD	No.§	Mean cost, USD	No.§	Mean cost, USD	No.§	Mean cost, USD	No.§	Mean cost, USD
No defect	3,571,404	4,804	416,265	25,979	398,395	14,516	951,630	14,670	16,658,885	13,099	**21,996,579**	**12,089**
Any defect	353,630	13,692¶	97,085	61,881	70,405	28,559	84,330	28,538	331,845	20,907	**937,295**	**23,690**
Cardiovascular, critical	5,965	79,481	11,440	128,700	5,380	79,335	3,770	63,332	5,825	34,105	**32,380**	**86,803**
Cardiovascular	40,095	46,527	41,690	85,846	21,490	45,754	15,720	44,526	90,050	30,043	**209,045**	**47,038**
Aortic valve stenosis	340	73,405	490	119,278	110	27,810	280	61,876	1,370	41,825	**2,590**	**62,196**
Atrial septal defect	—**	—**	15,680	63,964	9,490	42,483	5,095	35,458	45,570	31,479	**75,835**	**39,840**
Atrioventricular septal defect	1,180	104,798	2,820	117,756	1,030	60,301	515	52,148	520	27,665	**6,065**	**92,182**
Coarctation of aorta	1,720	71,865	2,525	135,489	615	46,094	570	45,512	1,680	31,249	**7,110**	**80,521**
Common truncus	185	141,256	205	130,074	130	161,151	155	66,602	135	50,004	**810**	**112,124**
Dextro-transposition of great arteries	855	83,149	1,295	170,533	480	79,142	310	55,015	660	37,539	**3,600**	**103,264**
Double outlet right ventricle	805	111,159	1,640	127,862	1,110	77,471	490	78,043	315	77,532	**4,360**	**102,714**
Ebstein anomaly	170	77,141	285	95,984	300	46,389	225	64,109	750	27,301	**1,730**	**51,611**
Hypoplastic left heart syndrome	915	121,117	2,075	150,444	1,470	73,969	945	92,979	380	74,707	**5,785**	**112,011**
Interrupted aortic arch	115	102,776	320	199,973	95	77,770	60	69,036	25	10,323	**615**	**142,438**
Pulmonary valve atresia	200	272,866	380	124,374	190	173,504	150	41,734	150	45,257	**1,070**	**138,177**
Single ventricle	340	155,126	1,010	166,406	750	66,991	485	61,920	515	42,193	**3,100**	**104,135**
Tetralogy of Fallot	1,365	73,218	3,050	117,165	920	126,979	735	52,117	1,210	29,541	**7,280**	**89,034**
Total anomalous pulmonary venous connection	270	106,042	760	189,531	230	55,991	115	65,213	75	21,751	**1,450**	**134,265**
Tricuspid valve atresia	300	92,262	660	81,529	430	83,806	205	53,565	440	24,579	**2,035**	**68,462**
Ventricular septal defect	19,100	35,719	12,555	77,434	4,415	38,583	2,025	39,583	4,900	26,875	**42,995**	**47,369**
CNS	13,865	52,329	11,600	71,978	14,400	24,901	19,005	28,716	38,940	18,127	**97,810**	**32,417**
Anencephaly	255	3,502	—**	—**	15	49,903	15	78,230	—**	—**	**285**	**9,877**
Encephalocele	265	33,206	315	64,542	120	24,526	205	66,508	1,745	25,496	**2,650**	**34,037**
Holoprosencephaly	330	48,100	430	52,217	615	22,643	550	34,333	175	21,945	**2,100**	**35,703**
Spina bifida without anencephaly	880	45,169	1,250	64,401	1,675	18,846	4,675	25,621	21,140	15,491	**29,620**	**20,225**
Chromosomal	8,210	46,993	10,995	75,070	15,225	26,372	15,235	28,578	31,785	18,281	**81,450**	**32,280**
Trisomy 13	265	35,177	285	63,489	180	24,873	200	48,340	170	36,940	**1,100**	**43,492**
Trisomy 18	585	56,072	520	106,796	450	37,366	230	31,700	405	18,974	**2,190**	**54,852**
Trisomy 21	4,700	37,462	6,225	59,353	6,740	20,740	5,425	23,676	19,955	16,716	**43,045**	**26,654**
Turner syndrome	455	20,837	185	66,991	210	37,083	435	25,589	2,360	17,867	**3,645**	**22,760**
Cleft lip, palate, or both	4,595	20,809	4,205	44,472	2,225	20,661	1,640	17,551	785	18,513	**13,450**	**27,651**
Cleft lip with cleft palate	1,965	23,733	1,805	49,534	795	17,313	1,000	15,135	340	20,581	**5,905**	**29,118**
Cleft lip without cleft palate	915	5,896	450	15,407	50	10,883	60	13,972	80	8,569	**1,555**	**9,258**
Cleft palate without cleft lip	1,715	25,414	1,950	46,493	1,380	22,944	580	22,086	365	18,765	**5,990**	**30,980**
Ear	13,050	10,005	1,715	77,822	710	31,595	715	26,105	315	19,229	**16,505**	**18,854**
Anotia or microtia	680	18,657	360	99,759	305	33,708	575	26,824	110	26,292	**2,030**	**38,028**
Eye	2,085	64,266	1,605	82,823	1,165	28,803	825	35,048	1,340	18,047	**7,020**	**50,367**
Anophthalmia or microphthalmia	255	68,830	345	66,729	210	20,661	130	34,154	160	16,837	**1,100**	**47,315**
Congenital cataract	235	24,404	190	61,187	160	41,027	135	22,791	265	11,517	**985**	**30,511**

See table footnotes on the next page.

TABLE 2. (*Continued*) Weighted national estimates of frequencies and mean costs of birth defect–associated hospitalizations* among persons aged <65 years, by selected specific birth defect and age group — National Inpatient Sample, United States, 2019

	Age group at admission, yrs											
	Birth hospitalization		<1, nonbirth		1–5		6–18		19–64		All age groups	
Birth defect†	No.§	Mean cost, USD	No.§	Mean cost, USD	No.§	Mean cost, USD	No.§	Mean cost, USD	No.§	Mean cost, USD	No.§	Mean cost, USD
GI	11,040	55,032	16,210	62,397	5,525	34,895	4,460	29,743	21,395	19,998	**58,630**	**40,463**
Biliary atresia	665	154,509	1,355	100,377	340	74,293	210	38,767	340	34,661	**2,910**	**97,576**
Esophageal atresia or tracheoesophageal fistula	845	66,710	920	214,651	255	51,169	110	47,589	790	26,491	**2,920**	**100,363**
Rectal and large intestinal atresia or stenosis	1,310	57,601	2,415	65,145	860	21,769	345	20,196	370	16,827	**5,300**	**49,943**
Small intestinal atresia or stenosis	1,100	88,157	1,055	151,120	325	31,938	145	24,159	185	17,017	**2,810**	**97,308**
Genitourinary	80,320	14,354	15,555	68,294	8,385	26,362	8,450	22,150	77,840	15,472	**190,550**	**20,088**
Congenital posterior urethral valves	220	55,495	565	73,936	325	28,558	365	32,728	130	42,875	**1,605**	**50,332**
Hypospadias	13,330	13,411	2,150	60,831	685	23,908	280	24,946	1,385	21,013	**17,830**	**20,304**
Renal agenesis or hypoplasia	2,150	23,577	1,185	64,522	1,155	45,675	1,680	22,996	13,370	17,399	**19,540**	**23,089**
Integumentary	158,620	6,788	5,760	79,162	2,310	22,121	3,505	26,692	14,970	19,479	**185,165**	**10,634**
MS	57,260	18,657	18,095	74,183	13,845	27,660	20,460	27,166	42,490	18,584	**152,150**	**27,204**
Clubfoot	8,215	14,914	1,810	89,692	1,315	20,961	1,445	20,056	2,100	16,226	**14,885**	**25,225**
Craniosynostosis	960	30,115	3,035	47,606	1,485	34,028	680	36,084	205	19,316	**6,365**	**39,658**
Diaphragmatic hernia	1,040	110,848	915	195,456	390	22,978	155	40,803	755	23,732	**3,255**	**100,562**
Gastroschisis	1,325	85,080	505	186,873	155	18,598	150	14,763	200	12,744	**2,335**	**91,969**
Limb deficiencies or reduction defects	1,125	21,628	350	70,995	495	31,571	655	26,979	790	18,491	**3,415**	**28,430**
Omphalocele	980	48,074	460	158,502	335	40,173	75	32,640	105	10,330	**1,955**	**70,084**
Other syndrome affecting multiple systems	1,725	66,503	3,555	92,066	4,560	31,502	5,065	28,560	14,145	21,905	**29,050**	**35,806**
Other defect	9,645	107,240	8,035	138,524	7,165	34,298	6,310	23,981	11,720	18,173	**42,875**	**64,313**

Abbreviations: CNS = central nervous system; GI = gastrointestinal; ICD-10-CM = *International Classification of Diseases, Tenth Revision, Clinical Modification*; MS = musculoskeletal; USD = U.S. dollars.

* Identified by scanning up to 40 available diagnosis code fields for ICD-10-CM diagnosis codes Q00–Q99: congenital malformations, deformations, and chromosomal abnormalities.

† Birth defects categories correspond to blocks of ICD-10-CM diagnosis codes: cardiovascular (Q20–Q28), CNS (Q00–Q07), chromosomal (Q90–Q99), cleft lip/palate (Q35–Q37), ear (Q16–Q17), eye (Q10–Q15), GI (Q38–Q45), genitourinary (Q50–Q64), integumentary (Q80–Q85), MS (Q65–Q79), and other syndrome (Q87). "Other defect" includes birth defects of the face and neck (Q18), respiratory system (Q30–Q34), and other congenital malformations (Q86 and Q89). Critical cardiovascular defects (https://www.cdc.gov/ncbddd/heartdefects/facts.html) were operationalized using the National Birth Defects Prevention Network Congenital Malformations Surveillance Report (https://www.nbdpn.org/docs/Birth_Defects_Data_and_Directory_2022.pdf). The specific defects included are only those defined in the National Birth Defects Prevention Network Congenital Malformations Surveillance Report; birth defects not included here contribute to frequencies and costs aggregated by birth defect category and overall.

§ Because a single hospitalization might include more than one specific birth defect, individual birth defect frequencies might sum to >100% of birth defects categories or overall frequencies, and mean costs multiplied by frequencies will correspondingly sum to >100% of total costs.

¶ For hospitalizations with any birth defect, the birth hospitalization costs include the costs for routine birth hospitalization.

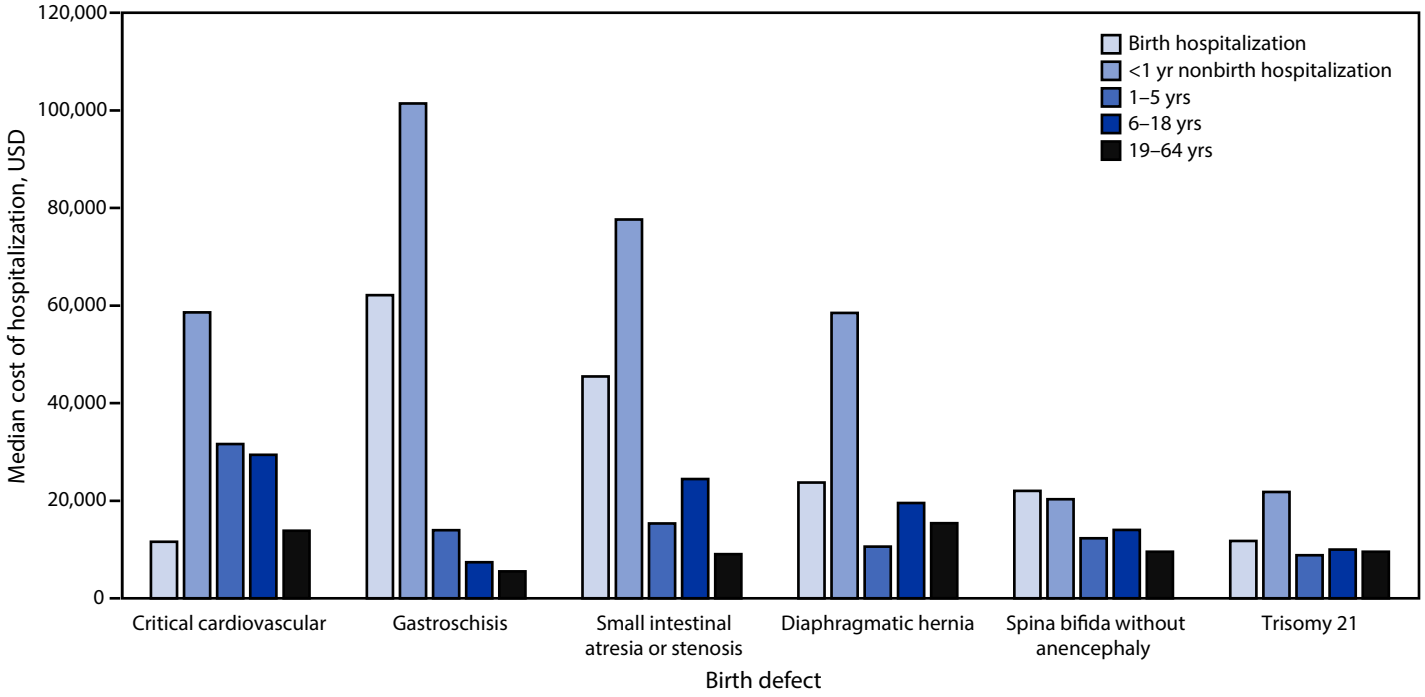
** Cell sizes ≤10 were suppressed. Sums across all ages exclude suppressed cells.

(Table 2) (Figure). Overall, nearly one third of hospitalization costs occurred among patients aged 19–64 years (Table 1).

Discussion

During 2019, the cost of hospitalizations for persons aged <65 years with a birth defect diagnosis code was estimated at $22.2 billion. These hospitalizations were associated with disproportionately high costs, constituting 4.1% of all hospitalizations among persons in the United States aged <65 years and 7.7% of total costs. Nearly one half of hospitalization costs associated with birth defects occurred among neonates and infants, and these costs disproportionately affected persons aged <1 year during nonbirth hospitalizations. Defects of the cardiovascular system were the most prevalent birth defects, were associated with disproportionately high ($9.8 billion) hospitalization costs, and included many of the costliest individual birth defects.

FIGURE. Weighted estimates of median costs of hospitalizations, by birth defect*,† and age group at admission — National Inpatient Sample, United States, 2019



Abbreviation: USD = U.S. dollars.

* Identified by scanning up to 40 available fields of *International Classification of Diseases, Tenth Revision, Clinical Modification* diagnosis codes. Critical cardiovascular defects include common arterial trunk (Q20.0), double outlet right ventricle (Q20.1), transposition of the great arteries (Q20.3), single ventricle (Q20.4), tetralogy of Fallot (Q21.3), pulmonary valve atresia (Q22.0), tricuspid valve atresia (Q22.4), Ebstein anomaly (Q22.5), hypoplastic left heart syndrome (Q23.4), coarctation of aorta (Q25.1), interrupted aortic arch (Q25.21), and total anomalous pulmonary venous connection (Q26.2). Specific birth defects are identified as gastroschisis (Q79.3), small intestinal atresia or stenosis (Q41), diaphragmatic hernia (Q79.0 and Q79.1), spina bifida without anencephaly (Q05, Q07.01, and Q07.03), and trisomy 21 (Q90).

† The specific birth defects shown were selected to represent a range of body systems.

Using 2013 NIS data, the total cost of birth defect–associated hospitalizations was estimated to be $22.9 billion for all ages and $19.1 billion for persons aged <65 years (*4*). Those estimates included adjustments for professional fees, which historically added 20%–25% to facility costs (*5*). Applying the same adjustments to the current estimates yields a 2019 estimate of $26.6–27.8 billion in total birth defect–associated hospitalization costs for persons aged <65 years. When adjusted to 2019 hospital care prices, the 2013 cost estimate is $21.0 billion for persons aged <65 years.** The share of birth defect–associated expenditures among total hospitalization expenditures was similar among all age groups: 5.2% in 2013 and 5.5% in 2019.

Limitations

The findings in this report are subject to at least five limitations. First, determining which costs are directly attributable to birth defects is challenging because of difficulties in identifying all sequelae of birth defects and their respective codes, the coding of minor birth defects, and the possible miscoding of some acquired structural or functional abnormalities as birth defects (*3*). Excluding hospitalizations for persons aged ≥65 years reduces the risk for miscoding but fails to identify the contribution of birth defects among this age group. Second, the potential for two or more birth defects to be documented during the same hospitalization could lead to overestimation of costs for findings presented by individual defect or category. Third, cost-to-charge ratios calculated at the hospital level do not necessarily accurately reflect the costs of different types of hospital services (*6*), which could bias estimates of a person's hospitalization costs in an unknown direction. Fourth, HCUP costs are limited to facility fees and fail to include physician or professional fees, thereby underestimating birth defect–associated hospitalization costs. Finally, it is difficult to distinguish the relationship between preterm birth and birth defects, and some of the birth defect–associated costs among preterm infants were possibly due to their prematurity rather than their birth defect.

Implications for Public Health Practice

Updated estimates of hospitalization costs for specific birth defects provide critical information about health care resource use. These data highlight the financial impact across the life

** https://meps.ahrq.gov/about_meps/Price_Index.shtml

Summary

What is already known about this topic?

Estimates of birth defect–associated hospitalization costs must be updated as detection, diagnosis, and treatment evolve for numerous birth defects.

What is added by this report?

During 2019, among patients aged <65 years, 4.1% of all hospitalizations and 7.7% of related inpatient medical costs were associated with birth defects. The total estimated cost of birth defect–associated hospitalizations was $22.2 billion.

What are the implications for public health practice?

These updated estimates of hospitalization costs illustrate the importance of continually determining the health care needs of persons with birth defects to ensure optimal health for all.

span and illustrate the need to understand the continued health care needs of persons born with birth defects to ensure optimal health for all.

Corresponding author: Justin Swanson, jswanson1@usf.edu.

[1]Lawton and Rhea Chiles Center for Healthy Mothers and Babies, College of Public Health, University of South Florida, Tampa, Florida; [2]Division of Birth Defects and Infant Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; [3]Office of the Director, National Center on Birth Defects and Developmental Disabilities, CDC; [4]Department of Economics, University of Utah, Salt Lake City, Utah.

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. Russell S. Kirby holds the Marrell endowed chair at the University of South Florida, College of Public Health and serves on the board of directors for the National Birth Defects Prevention Network. Jason L. Salemi and Jean Paul Tanner report grant support to the Florida Department of Health, subcontracted to the University of South Florida, for Advancing Population-based Surveillance of Birth Defects. No other potential conflicts of interest were disclosed.

References

1. CDC. Update on overall prevalence of major birth defects—Atlanta, Georgia, 1978–2005. MMWR Morb Mortal Wkly Rep 2008;57:1–5. PMID:18185492
2. Ely DM, Driscoll AK. Infant mortality in the United States, 2019: data from the period linked birth/infant death file. Natl Vital Stat Rep 2021;70:1–18. PMID:34878382 https://doi.org/10.15620/cdc:111053
3. Rodriguez FH 3rd, Raskind-Hood CL, Hoffman T, et al. How well do ICD-9-CM codes predict true congenital heart defects? A Centers for Disease Control and Prevention–based multisite validation project. J Am Heart Assoc 2022;11:e024911. PMID:35862148 https://doi.org/10.1161/JAHA.121.024911
4. Arth AC, Tinker SC, Simeone RM, Ailes EC, Cragan JD, Grosse SD. Inpatient hospitalization costs associated with birth defects among persons of all ages—United States, 2013. MMWR Morb Mortal Wkly Rep 2017;66:41–6. PMID:28103210 https://doi.org/10.15585/mmwr.mm6602a1
5. Peterson C, Xu L, Florence C, Grosse SD, Annest JL. Professional fee ratios for US hospital discharge data. Med Care 2015;53:840–9. PMID:26340662 https://doi.org/10.1097/MLR.0000000000000410
6. Salemi JL, Comins MM, Chandler K, Mogos MF, Salihu HM. A practical approach for calculating reliable cost estimates from observational data: application to cost analyses in maternal and child health. Appl Health Econ Health Policy 2013;11:343–57. PMID:23807539 https://doi.org/10.1007/s40258-013-0040-2

Status of New Vaccine Introduction — Worldwide, 2016–2021

Gurpreet Kaur, MD[1,2]; Rebecca M. Casey, MBBS[2]; Jaymin C. Patel, PhD[2]; Paul Bloem, MBA[3]; Jenny A. Walldorf, MD[3]; Terri B. Hyde, MD[2]

Abstract

This report describes the status of introductions globally for eight World Health Organization (WHO)–recommended new and underutilized vaccines, comprising 10 individual vaccine antigens. By 2021, among 194 countries worldwide, 33 (17%) provided all of these 10 WHO-recommended antigens as part of their routine immunization schedules; only one low-income country had introduced all of these recommended vaccines. Universal hepatitis B birth dose; human papillomavirus vaccine; rotavirus vaccine; and diphtheria, tetanus, and pertussis–containing vaccine first booster dose have been introduced by 57%, 59%, 60%, and 72% of all countries worldwide, respectively. Pneumococcal conjugate vaccine, rubella-containing vaccine, measles-containing vaccine second dose, and *Haemophilus influenzae* type b vaccine have been introduced by 78%, 89%, 94%, and 99% of all countries, respectively. The annual rate of new vaccine introductions declined precipitously when the COVID-19 pandemic started, from 48 in 2019 to 15 in 2020 before rising to 26 in 2021. Increased efforts to accelerate new and underutilized vaccine introductions are urgently needed to improve universal equitable access to all recommended vaccines to achieve the global Immunization Agenda 2021–2030 (IA2030) targets.

Introduction

The global Immunization Agenda 2021–2030 (IA2030), by increasing equitable access to and use of new and existing vaccines, envisions a world where everyone everywhere fully benefits from vaccines. IA2030, endorsed by the World Health Assembly, includes a target to achieve 500 new and underutilized vaccine introductions in low-income and middle-income countries' routine immunization schedules by 2030 (*1*). This report updates a 2016 report (*2*) and describes the status of introductions globally for eight World Health Organization (WHO)–recommended new and underutilized vaccines, comprising 10 individual vaccine antigens, including five provided beyond the first year of life.

Methods

Data on the status of national introductions of eight WHO-recommended new and underutilized vaccines in 194 countries were obtained from the WHO/UNICEF Immunization database (*3*); five of these vaccines are provided during infancy (hepatitis B birth dose [HepB-BD], *Haemophilus influenzae* type b vaccine [Hib], pneumococcal conjugate vaccine [PCV], rubella-containing vaccine [RCV], and rotavirus [RV] vaccine), and three vaccines including a total of five antigens are provided after the first year of life (fourth diphtheria, tetanus, and pertussis-containing vaccine [first booster] dose [DTPCV4],* human papillomavirus vaccine [HPV], and measles-containing vaccine second dose [MCV2]) (*4*). The number of new vaccine introductions globally was calculated for each year during 2016–2021 and compared with average number of annual new vaccine introductions during 2010–2015. Vaccine introduction status is additionally reported according to country income category as defined by the World Bank† (*5*).

Results

New and Underutilized Vaccines Included in National Schedules by 2021

By the end of 2021, among 194 countries, universal HepB-BD was included in the national immunization schedules in 111 (57%) countries, RV in 116 (60%), PCV in 152 (78%), and RCV in 173 (89%). HepB-BD, targeting only select populations, was included in the routine immunization schedules of 24 (12%) countries, mostly in the WHO European Region (EUR) (20 of 24 countries). Hib vaccine was included in the national immunization schedules of all but two (99%) countries (China and Russia). Beyond the first year of life, HPV vaccine, DTPCV4, and MCV2 were included in the national immunization schedules of 114 (59%), 140 (72%), and 183 (94%) countries, respectively.

New and Underutilized Vaccine Introductions, 2016–2021

During 2016–2021, among vaccines recommended during the first year of life, the numbers and percentage of countries that had implemented national vaccine introduction increased most for RV vaccine, from 84 (43%) countries to 116 (60%) (Table) (Supplementary Figure, https://stacks.cdc.gov/view/cdc/130137). During 2016–2021, among vaccines provided during the second year of life and beyond, the number of new

* DTPCV4 refers to the fourth dose of diphtheria, tetanus, and pertussis–containing vaccine administered at any age. DTPCV4 is one vaccine composed of three antigens.

† Country income categories were defined using the 2022 World Bank income classification except for Cook Islands, Niue, and Venezuela. Cook Islands is classified as high-income, and Niue is classified as middle-income based on Central Intelligence Agency classification (https://www.cia.gov/the-world-factbook/countries). Venezuela is classified as middle-income based on that country's most recent World Bank classification (2019).

TABLE. Number and percentage of countries that included eight World Health Organization–recommended new and underutilized vaccines* available in their national routine immunization schedule, by year — worldwide, 2016–2021

Year	No. (%), yr WHO recommended†							
	DTPCV4 2017§	HepB-BD 2009	Hib 2006	HPV 2009¶	MCV2 2009	PCV 2007	RCV 2000**	RV 2009
2016	135 (70)	100 (52)	190 (98)	69 (36)	164 (85)	132 (68)	155 (80)	84 (43)
2017	136 (70)	104 (54)	190 (98)	79 (41)	167 (86)	135 (70)	160 (82)	91 (47)
2018	137 (71)	106 (55)	191 (98)	87 (45)	171 (88)	138 (71)	168 (87)	95 (49)
2019	138 (71)	109 (56)	192 (99)	103 (53)	177 (91)	144 (74)	173 (89)	105 (54)
2020	137 (71)	110 (57)	192 (99)	107 (55)	179 (92)	146 (75)	173 (89)	111 (57)
2021	140 (72)	111 (57)	192 (99)	114 (59)	183 (94)	152 (78)	173 (89)	116 (60)

Abbreviations: DTPCV4 = first booster dose of diphtheria, tetanus, and pertussis–containing vaccine; HepB-BD = universal hepatitis B vaccine birth dose; Hib = *Haemophilus influenzae* type b vaccine; HPV = human papillomavirus vaccine; MCV2 = second dose of measles-containing vaccine; PCV = pneumococcal conjugate vaccine; RCV = rubella-containing vaccine; RV = rotavirus vaccine; WHO = World Health Organization.

* Vaccine introduction data for DTPCV4 was unavailable for 2016. For all other vaccines, no value indicates no introductions occurred for that year.

† Year WHO recommended inclusion of vaccine in all national routine immunization programs.

§ In 2017, WHO revised its DTPCV booster recommendations, shifting the first booster dose of tetanus to the second year of life to align with the recommendation for the first booster dose of pertussis. Countries reporting inclusion of DTPCV4 in this table might provide it at any age.

¶ HPV was originally recommended as a 3-dose schedule for girls aged 9–13 years in 2009 and updated to a 2-dose schedule recommendation in 2014 for girls aged 9–14 years; an alternative single-dose schedule was recommended in 2022 for girls aged 9–14 years.

** In 2000, WHO recommended introduction of RCV in countries where it can be safely introduced.

HPV vaccine introductions was higher than the number of introductions of any other recommended vaccine; the number of countries that had introduced HPV vaccine nationally increased 65%, from 69 countries in 2016 to 114 in 2021. During the same period, the number of countries that had introduced MCV2 increased by 12%, from 164 countries in 2016 to 183 in 2021; countries introducing DTPCV4 increased by 4%, from 135 countries in 2016 to 140 in 2021. By 2021, 33 (17%) of 194 countries provided all eight of these WHO-recommended new and underutilized vaccines as part of the routine immunization schedule; 56 (29%) countries had included all five vaccines recommended during the first year of life.

During 2016–2021, an average of 31 new introductions of these eight WHO-recommended new and underutilized vaccines occurred annually (representing a decline in introductions of approximately one third [34%]), compared with an average 47 new introductions annually during 2010–2015.§ The annual number of new vaccine introductions declined sharply at the start of the COVID-19 pandemic, from 48 in 2019 to 15 in 2020 (Figure 1). In 2021, there were 26 vaccine introductions, including one HepB-BD, three DTPCV4, six PCV, five RV, four MCV2, and seven HPV introductions.

New and Underutilized Vaccine Introductions, by World Bank Income Status and WHO Region

By 2021, among 28 low-income countries, 20 (71%) had yet to introduce HPV vaccine into their routine immunization schedule compared with 53 (50%) of 107 middle-income countries and seven (12%) of 59 high-income countries (Figure 2). RV vaccine had not yet been introduced in 25%, 39%, and 49% of low-, middle- and high-income countries, respectively. As well, minimal progress toward DTPCV4 and HepB-BD vaccine introductions was made across all country income categories during 2016–2021.

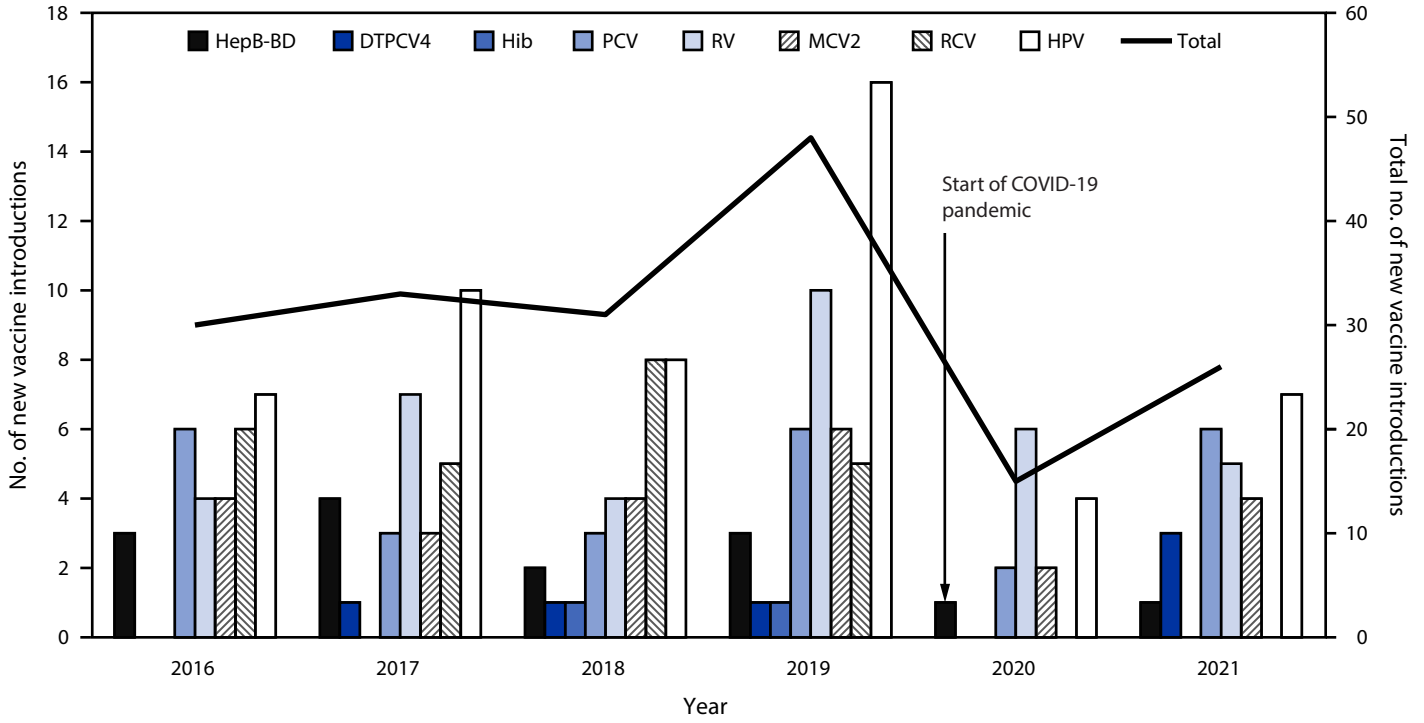
Among the 152 vaccine introductions implemented during 2016–2021, 58 (38%) were in the African Region (AFR); 28 (18%) in the Region of the Americas (AMR); 23 (15%) in the Western Pacific Region (WPR); 21 (14%) in EUR; 17 (11%) in the South-East Asia Region (SEAR); and five (3%) in the Eastern Mediterranean Region (EMR). As of 2021, by vaccine, the largest proportion of countries that had not introduced HepB-BD (72%), DTPCV4 (79%), MCV2 (19%), and RCV (34%) were in AFR. Among 21 countries in EMR, 19 (90%) had yet to introduce HPV vaccine. By schedule, an average of 29% of countries in AFR had yet to introduce one or more of five WHO-recommended infant vaccines followed by 27% in SEAR, 25% in EUR, 22% in EMR, 20% in AMR, and 14% in WPR. Beyond the infant schedule, an average of 51% countries in AFR had yet to introduce at least one of HPV, DTPCV4, or MCV2 into the national immunization schedule, followed by 40% in EMR, 30% in SEAR, 23% in WPR, 9% in EUR, and 4% in AMR.

Discussion

Worldwide, the introduction of WHO-recommended vaccines into national immunization schedules has increased overall since 2016; however, the rate of new vaccine introductions slowed during the COVID-19 pandemic. More than two thirds of the 194 WHO member countries have now individually introduced Hib vaccine (99%), MCV2 (94%), RCV (89%),

§ Introduction data for DTPCV4 are not available in average calculation for 2012, 2013, 2015, and 2016.

FIGURE 1. Number of countries with new vaccine introductions, by vaccine and year — worldwide,* 2016–2021



Abbreviations: DTPCV4 = first booster dose of diphtheria, tetanus, and pertussis–containing vaccine; HepB-BD = hepatitis B vaccine birth dose; Hib = *Haemophilus influenzae* type b vaccine; HPV = human papillomavirus vaccine; MCV2 = second dose of measles-containing vaccine; PCV = pneumococcal conjugate vaccine; RCV = rubella-containing vaccine; RV = rotavirus vaccine.
* Vaccine introduction data for DTPCV4 was unavailable for 2016. For all other vaccines, no value indicates no introductions occurred for that year.

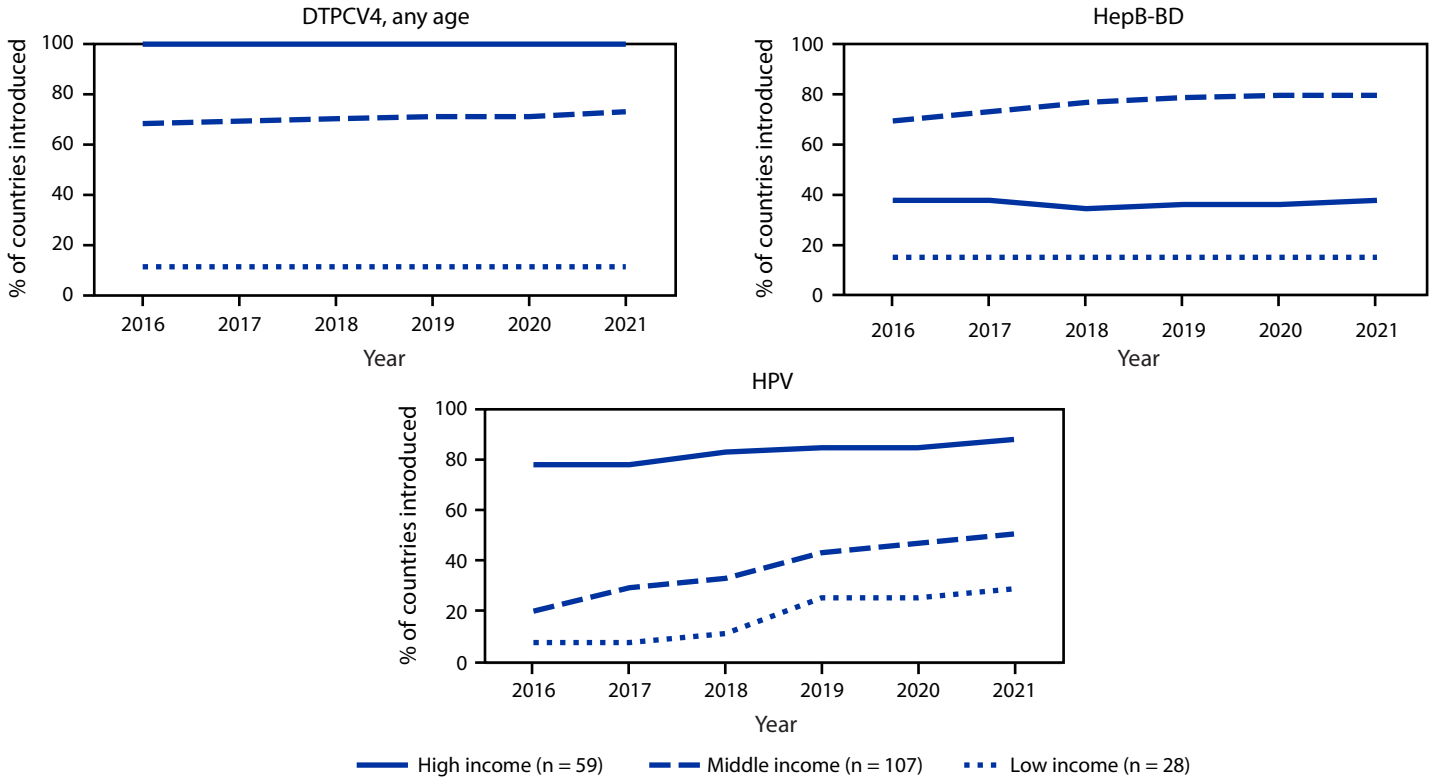
PCV (78%), and DTPCV4 (72%). In low-income countries, DTPCV4, HepB-BD, and HPV vaccine are the most underutilized vaccines, whereas in high-income countries, RV vaccine is the most underutilized vaccine. Enhanced efforts are needed to revitalize national vaccine introductions and prioritize equitable access to all vaccines, including those provided beyond infancy, through adolescence, and across the life-course.

A reliable supply of affordable vaccines is required to facilitate new vaccine introductions and achieve high vaccination coverage to achieve the goals outlined in the IA2030, which include achieving at least 500 cumulative vaccine introductions in low- and middle-income countries by 2030; as of 2021, 167 cumulative vaccine introductions had been achieved (*1*). During the last 5 years, availability of RV and HPV vaccines has suffered from supply constraints, which have affected vaccine introductions; these constraints have been exacerbated by the COVID-19 pandemic (*4*,*6*). Global partners including Gavi, the Vaccine Alliance, have been working to address challenges around supply and affordability so that the growing portfolio of newly licensed vaccines can be introduced worldwide more rapidly.

In 2016, Gavi began providing support for the national scale-up of HPV vaccine introductions in low- and middle-income countries after small-scale subnational demonstration projects during 2011–2015 determined that introduction was feasible. Despite vaccine supply challenges, the percentage of countries that had introduced HPV vaccine into national programs during 2016–2021 increased by 65%, which is more than the global increase in introductions for any other vaccine. Fifty-seven low- and middle-income countries qualified for Gavi support during 2016–2021, but this support was limited to low- and lower-middle-income countries. Among middle-income countries, which can be further subdivided into lower-middle-income and upper-middle-income, no upper-middle-income countries qualified for Gavi support during 2016–2021. As a result of the COVID-19 pandemic, Gavi paused its investment in certain vaccines (such as DTPCV4 and HepB-BD), which hindered progress for those vaccines introductions (*7*,*8*).

The vaccine access challenges in middle-income countries and the need for increased action have been subjects of increasing focus. Middle-income countries still report that the cost of vaccines is a major obstacle to their introduction, in part because of a lack of procurement capacity and suboptimal in-country regulatory processes (*1*). In December 2020, Gavi approved a new approach to engaging with middle-income countries that were formerly Gavi-eligible and selected countries that have never been Gavi-eligible to drive the sustainable introduction of important vaccines that have not yet been

FIGURE 2. Percentage of countries that introduced selected World Health Organization–recommended vaccines* into their national immunization schedule, by income status† — worldwide, 2016–2021



Abbreviations: DTPCV4 = first booster dose of diphtheria, tetanus, and pertussis–containing vaccine; HepB-BD = hepatitis B vaccine birth dose; HPV = human papillomavirus vaccine; USD = U.S. dollars.

* Vaccines with lowest introduction in low-income countries' national immunization schedules as of 2021. HepB-BD indicates the introduction of universal HepB-BD into the national immunization schedule. In addition, 24 countries had implemented HepB-BD selective introduction, of which 22 were high-income and two were middle-income countries.

† Country income categories were defined using the 2022 World Bank income classification except for Cook Islands, Niue, and Venezuela. Cook Islands is classified as high-income and Niue is classified as middle-income based on Central Intelligence Agency classification (https://www.cia.gov/the-world-factbook/countries/) Venezuela is classified as middle-income based on that country's most recent World Bank classification (2019). Gross national income: low income <1,085 USD; middle income = 1,086–13,205 USD; and high income >13,205 USD.

introduced, including HPV and RV vaccines. In addition, in 2022, WHO recommended that HPV vaccination may optionally be delivered as a single dose vaccine (*4*), which will likely increase programmatic feasibility and flexibility and reduce cost. These efforts to improve targeted donor funding and timely evidence-based updates to global vaccination policy are critical to ensuring continued progress in successful new vaccine introductions worldwide.

The delayed introduction of RV vaccine in high-income countries suggests that challenges beyond vaccine cost or interrupted supply, such as the lack of awareness among policymakers about the benefits of RV vaccine against the impact of rotavirus-related disease, and the lasting negative impact of safety concerns (*9*) are affecting introductions. Given the evidence that the benefits of RV vaccine far exceed the risks in low-, middle-, and high-income countries (*9*), high-level advocacy is needed globally to encourage the prioritization of RV vaccine and other underutilized vaccines. Additions to the evidence base supporting safety and effectiveness of these vaccines in specific contexts can further drive demand and support for these vaccine introductions into country routine immunization schedules. To accelerate global access to DTPCV4 and HepB-BD, targeted funding to support introductions, innovative strategies to address country awareness, and logistical support (e.g., trained staff members and cold chain management) to ensure timely access to vaccination, are needed (*9,10*).

Limitations

The findings in this report are subject to at least three limitations. First, routine immunization schedule data reported by countries to WHO and UNICEF might not reflect national availability of vaccine. Second, incomplete data reported for some vaccines (e.g., DTPCV4 for years 2012, 2013, 2015, and

Summary

What is already known about this topic?

The global Immunization Agenda 2021–2030 (IA2030) aims to increase equitable access to and use of new and existing vaccines. The COVID-19 pandemic caused widespread disruption to routine immunization services.

What is added by this report?

By 2021, 17% of countries worldwide provided all eight World Health Organization–recommended new and underutilized vaccines in their routine immunization schedules. The number of new vaccines added to a national immunization program declined sharply at the start of the COVID-19 pandemic, from 48 in 2019 to 15 in 2020.

What are the implications for public health practice?

To achieve IA2030 targets, increased efforts to accelerate introductions of new and underutilized vaccines are urgently needed to facilitate equitable access, including to vaccines delivered beyond the first year of life.

2016) limited the accuracy of the annual number of vaccine introductions for these years. Finally, World Bank income classification was not available for all countries, so alternative data sources or alternative years were used in calculations.

Implications for Public Health Practice

It is encouraging that, despite the disruptions to essential health services during the COVID-19 pandemic, many countries continued to introduce vaccines into their national schedules during 2020–2021. However, the COVID-19 pandemic slowed progress, and urgent recovery actions are needed. The COVID-19 vaccination response during the pandemic has highlighted the importance of building strong vaccination delivery platforms through childhood and across the life-course. To achieve IA2030 targets, increased efforts to accelerate introductions of new and underutilized vaccines are urgently needed to facilitate equitable access, including access to vaccines delivered beyond the first year of life.

Corresponding author: Gurpreet Kaur, tqz0@cdc.gov.

[1]Epidemic Intelligence Service, CDC; [2]Global Immunization Division, Center for Global Health, CDC; [3]Department of Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland.

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

References

1. World Health Organization. Immunization agenda 2030: a global strategy to leave no one behind. Geneva, Switzerland: World Health Organization; 2020. https://immunizationagenda2030.org
2. Loharikar A, Dumolard L, Chu S, Hyde T, Goodman T, Mantel C. Status of new vaccine introduction—worldwide, September 2016. MMWR Morb Mortal Wkly Rep 2016;65:1136–40. PMID:27764083 https://doi.org/10.15585/mmwr.mm6541a3
3. World Health Organization. Immunization dashboard. Geneva, Switzerland: World Health Organization; 2023. Accessed June 2, 2023. https://immunizationdata.who.int
4. World Health Organization. Table 1: summary of WHO position papers—recommendations for routine immunizations. Geneva, Switzerland: World Health Organization; 2023. https://cdn.who.int/media/docs/default-source/immunization/immunization_schedules/table_1_feb_2023_english.pdf?sfvrsn=c7de0e97_11&download=true
5. World Bank. World Bank country classifications. Washington, DC: World Bank; 2022. Accessed June 2, 2023. https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fdatacatalogfiles.worldbank.org%2Fddh-published%2F0037712%2FDR0090755%2FCLASS.xlsx&wdOrigin=BROWSELINK
6. UNICEF Supply Division. Rotavirus vaccine: supply and demand. New York, NY: UNICEF; 2022. https://www.unicef.org/supply/media/10841/file/Rotavirus-Vaccine-Supply-Demand-Update-January-2022.pdf
7. Ward J. Opinion: here's why Gavi must start hepatitis B vaccination in Africa. Washington, DC: Devex; 2023. https://www.devex.com/news/opinion-here-s-why-gavi-must-start-hepatitis-b-vaccination-in-africa-105314#.ZEbvme4UNl4.mailto
8. Gavi. Vaccine investment strategy 2024. Geneva, Switzerland: Gavi; 2023. https://www.gavi.org/our-alliance/strategy/vaccine-investment-strategy-2024#update
9. Cohen R, Martinón-Torres F, Posiuniene I, Benninghoff B, Oh KB, Poelaert D. The value of rotavirus vaccination in Europe: a call for action. Infect Dis Ther 2023;12:9–29. PMID:36355309 https://doi.org/10.1007/s40121-022-00697-7
10. World Health Organization. Hepatitis B vaccines: WHO position paper—July 2017. Wkly Epidemiol Rec 2017;92:369–92. PMID:28685564

Notes from the Field

Doubling of Cyclosporiasis Cases Partially Attributable to a Salad Kit — Florida, 2021–2022

Paul Rehme, DVM[1]

Cyclosporiasis is a gastrointestinal infection caused by a protozoan parasite, *Cyclospora cayetanensis*. This species is only known to infect humans and is acquired when oocysts are ingested through food or water contaminated with feces that contain the parasite. The illness was first reported in 1979, and the organism was identified and named in 1994 (*1*). Historically, infections were typically acquired outside of the United States or from produce that was imported into the United States (*1*). In recent years, the number of reported U.S. cases has been increasing: cases more than doubled from 537 in 2016 to 1,194 in 2017, and then nearly tripled, to 3,519 cases in 2018; in 2019, 4,703 cyclosporiasis cases were reported.* Recently, the parasite has been found on domestically grown produce (*2*), and infections have been attributed to these foods (*3*). Produce washing will decrease but not eliminate the parasite (*1*).

Investigation and Outcomes

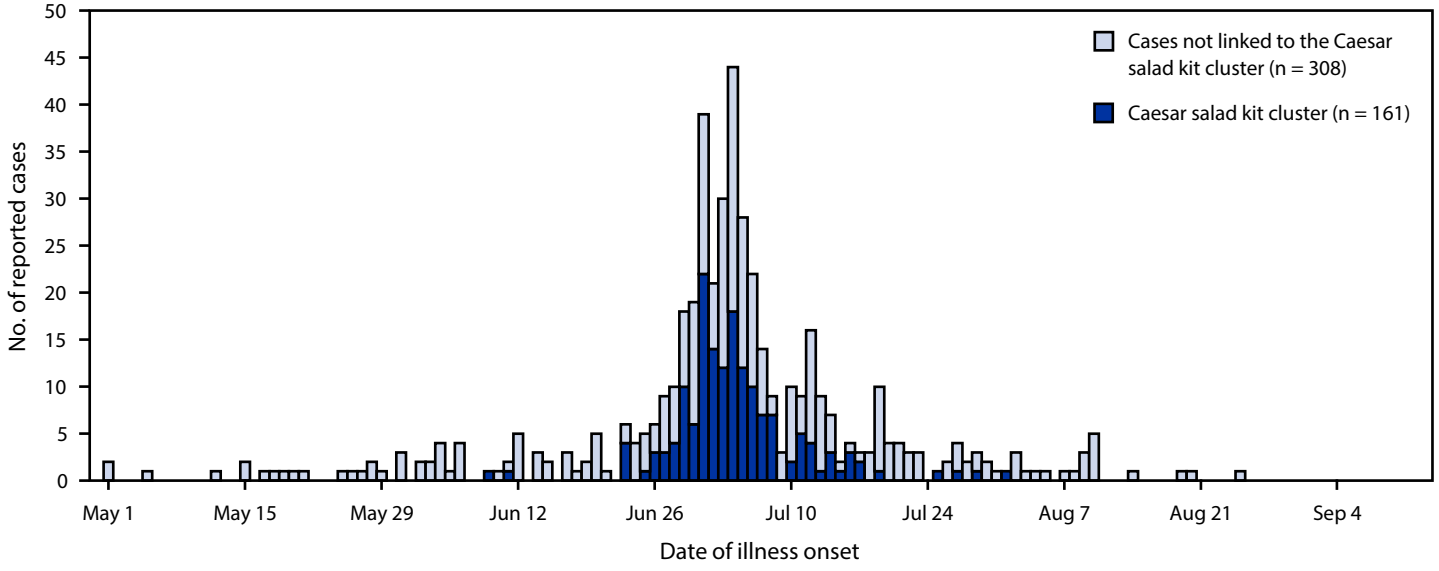
In Florida, reported numbers of cyclosporiasis cases have been increasing over the last 10 years†; 254 cases were reported in Florida in 2021, and the number doubled to 513 in 2022, including 486 (95%) laboratory-confirmed cases and 27 (5%) probable cases. Specimens from 276 (54%) cyclosporiasis patients were submitted to CDC's *Cyclospora* genotyping project, including 211 (76%) which were matched to a specific temporal-genetic cluster code§ (*4*). Among the 513 cases reported in 2022, 469 (91%) patients reported illness onset during May 1–August 31, 2022, with a peak in early July (Figure).

The Florida Department of Health required that county public health personnel complete the CDC Cyclosporiasis National Hypothesis Generating Questionnaire (CNHGQ)¶ for all patients with illness onset dates during May 1–August 31, 2022. Among 457 completed questionnaires 330 (72%) respondents reported exposure information with no international travel, including 200 (61%) who reported exposure to bagged salad, a commercially produced package of prewashed salad greens. Among respondents reporting exposure to bagged salad, 85 (43%) noted a specific brand of Caesar salad kit containing only romaine lettuce, from a specific grocery store chain. Onset

* https://wonder.cdc.gov/nndss-annual-summary.html
† https://www.flhealthcharts.gov/charts/CommunicableDiseases/default.aspx

§ Collection of genetically linked specimens within the same 2-week period were initially assigned temporal-genetic cluster codes, after which a sliding window was applied such that the earliest and latest collection dates could be adjusted to account for specimens that were not collected within the initial 2-week period assigned to the temporal-genetic cluster, but which were genetically linked to the cluster. This process is continued until genetically linked specimens are not detected 7 days before or after the latest dates and allows for the time required for patients to submit specimens after illness onset.
¶ https://www.cdc.gov/parasites/cyclosporiasis/resources/pdf/CNHGQ_2021.pdf

FIGURE. Cyclosporiasis cases (N = 469) — Florida, May 1–August 31, 2022



dates for this case cluster occurred during June 23–July 16, with a median disease onset date of July 1. An additional 76 persons with cyclosporiasis reported exposure to Caesar salad kits, but these persons either could not recall the salad kit brands or had purchased them from a different chain for a total of 161 potentially linked cases. Outbreaks of cyclosporiasis have been previously linked to bagged salads in the past (*4*). This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.**

CDC uses a genotyping tool to aid epidemiologic case linkage in near-real time. Among 211 successfully genotyped specimens from Florida, 153 (73%) were assigned to the same temporal genetic cluster (2022_001), including 43 (96%) of 45 genotyped specimens linked to the bagged salad cluster and 30 (39%) of the 76 persons reporting Caesar salad kits with no further identifying information. This information was shared with the Food and Drug Administration along with source information for the implicated product from the grocery store chain to facilitate traceback of the product; however, the source of the likely contaminated product was not identified.

Preliminary Conclusions

In this investigation, results from genotyping analysis demonstrated strong agreement between the genotyping and epidemiologic data. The combination of the completed CNHGQ and genetic data strengthens evidence for identifying cases potentially linked to the same source of infection and can guide future investigations.

** 45 C.F.R. part 46.102(I)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241 (d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq

Acknowledgment

Parasitic Disease Branch, Division of Parasitic Diseases and Malaria, Global Health, CDC.

Corresponding author: Paul Rehme, paul.rehme@flhealth.gov.

[1]Florida Department of Health.

The author has completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

References

1. Ortega YR, Sanchez R. Update on *Cyclospora cayetanensis*, a food-borne and waterborne parasite. Clin Microbiol Rev 2010;23:218–34. PMID:20065331 https://doi.org/10.1128/CMR.00026-09
2. Beach C. FDA documents first *Cyclospora* contamination of U.S. fresh produce. Seattle, WA: Food Safety News; 2018; https://www.foodsafetynews.com/2018/09/fda-documents-first-cyclospora-contamination-of-u-s-fresh-produce/
3. Hoang LMN, Fyfe M, Ong C, et al. Outbreak of cyclosporiasis in British Columbia associated with imported Thai basil. Epidemiol Infect 2005;133:23–7. PMID:15724706 https://doi.org/10.1017/S0950268804003176
4. Barratt J, Ahart L, Rice M, et al. Genotyping *Cyclospora cayetanensis* from multiple outbreak clusters with an emphasis on a cluster linked to bagged salad mix—United States, 2020. J Infect Dis 2022;225:2176–80. PMID:34606577 https://doi.org/10.1093/infdis/jiab495

Notes from the Field

Scrub Typhus Outbreak — Los Lagos Region, Chile, January–February 2023

Thomas Weitzel, MD[1,2,*]; Constanza Martínez-Valdebenito, MSc[3,4,*]; Gerardo Acosta-Jamett, PhD[5]; Katia Abarca, MD[3,4]

During January 14–February 14, 2023, a total of 36 cases of suspected scrub typhus were reported from the Los Lagos Region in southern Chile. Scrub typhus is a bacterial disease caused by one of three *Orientia* spp. and transmitted through bites from infected chiggers (larval mites).

Investigation and Outcomes

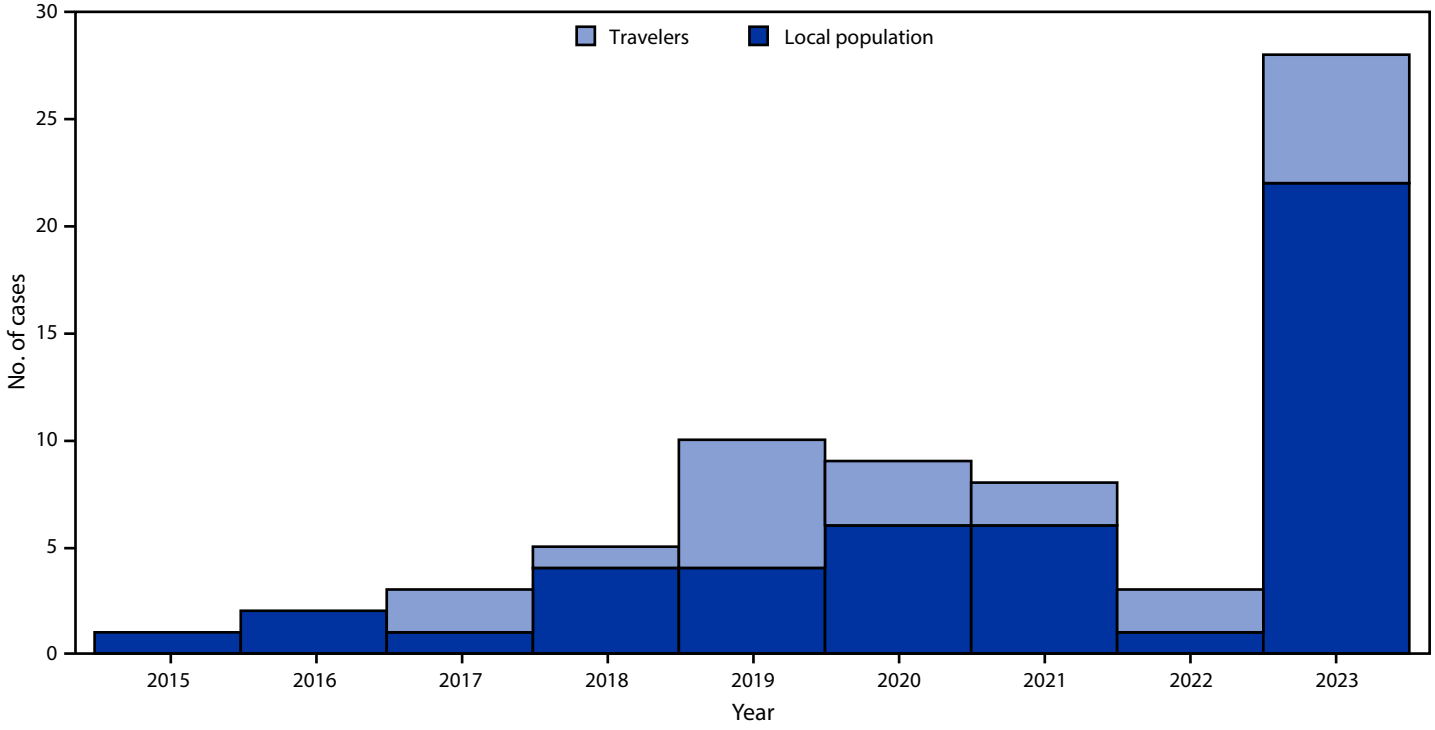
Patients with reported cases fulfilled at least two of the following three criteria in the Chilean surveillance case definition: 1) acute febrile illness; 2) a generalized maculopapular rash; and 3) presence of a necrotic lesion (eschar). Blood and eschar material collected from patients with suspected scrub typhus cases were sent to the national reference laboratory in Santiago and tested using genus-specific quantitative real-time polymerase chain reaction (qPCR) testing (Orien16S), which detects all known *Orientia* species (*1*). Demographic and clinical data were collected by the treating physicians using the national surveillance system questionnaire. This study was reviewed and approved by the Pontificia Universidad Católica Institutional Review Board.[†]

In 28 (78.0%) of the 36 suspected cases, *Orientia* spp. was identified by qPCR, including 16 (57.0%) from eschar material only, one (4.0%) from the buffy coat fraction of the collected blood specimen only, and 11 (39.0%) from both sources. Twenty-two (79.0%) confirmed cases were acquired at the patients' place of residence, and six (21.0%) were acquired during travel in the Los Lagos Region. The number of confirmed cases reported in the Los Lagos Region as of February 2023 represented an increase of nearly 450% over the mean number of cases reported during the preceding 8 years (5.1) (Figure). Most confirmed cases occurred among males (64.3%); two thirds (67.9%) occurred among adults aged 18–50 years (median age = 46 years; range = 8–71 years). The typical clinical presentation included fever (85.7%), accompanied by skin manifestations (eschar [100.0%] or maculopapular rash [89.3%]), as well as nonspecific signs and symptoms including headache (85.7%), myalgias (78.6%), chills (75.0%), and night sweats (57.1%). Among patients for whom laboratory

[*] These authors contributed equally to this report.

[†] C.F.R. part 46; 21 C.F.R. part 56.

FIGURE. Reported scrub typhus cases by affected population — Los Lagos Region, Chile, January 14–February 14, 2015–2023



data were available, abnormalities included elevated transaminases in 96.0% (21 of 22), C-reactive protein in 84.0% (16 of 19), thrombocytopenia in 22.0% (five of 23), and leukopenia in 30.0% (seven of 23). Twenty-six (93.0%) patients reported contact with vegetation or firewood during domestic (42.0%), occupational (30.0%), or leisure (19.0%) activities. All patients received doxycycline treatment and recovered without complications.

Preliminary Conclusions

Scrub typhus is the oldest known vectorborne infection, and until recently, has almost exclusively been reported from certain regions within the Asia-Pacific region (the tsutsugamushi triangle), where it is caused by *Orientia tsutsugamushi* (*2*). In that region, approximately 1 million cases are reported each year, with a case fatality rate of approximately 7% if not adequately treated (*2*). Scrub typhus was recently discovered in southern Chile (*3*), occurring over a geographic range of almost 1,240 miles (2,000 km) from the Biobío Region in central Chile to Tierra del Fuego in the south. Molecular analyses have identified a novel *Orientia* species (*Candidatus* Orientia chiloensis) as the causative pathogen (*4*). Vector studies in the Los Lagos and Aysén regions suggested larval trombiculid mites of the genus *Herpetacarus* (commonly known in the United States as chiggers) as disease vectors (*5*).

Understanding the reasons for the observed increase in scrub typhus cases requires further eco-epidemiologic studies. Scrub typhus in Chile displays a marked seasonality, with 97% of cases to date occurring during the austral summer months of December–March (Chilean Rickettsia and Zoonosis Research Group, unpublished data, January 2023). Apart from climatic factors, the outbreak might also be related to an increase in outdoor activities after 2 years of pandemic restrictions as well as growing awareness of the disease, resulting in increased testing and reporting. Because of its nonspecific clinical characteristics, scrub typhus might be easily overlooked, and diagnosis requires a high index of suspicion. Rapid diagnosis and treatment, however, are crucial to avoid severe disease and possible complications, such as pneumonia, renal failure, and meningoencephalitis. If infection is suspected, treatment with doxycycline should be initiated without delay (*2*).

Exposure to trombiculid mites is associated with outdoor activities and affects not only residents of rural areas, but also travelers on camping and trekking trips. The growth of ecotourism in southern Chile has increased the importance of raising awareness among physicians worldwide who see ill travelers returning from the region. No vaccine is available to prevent scrub typhus; to prevent exposure to mites, travelers should avoid contact with lower vegetation and soil, wear long sleeves and pants, treat boots and clothing with the insecticide permethrin (0.5%), and use insect repellents containing DEET or other active ingredients registered by the Environmental Protection Agency for use against chiggers, on exposed skin and clothing (*2*).

Acknowledgments

The National Research and Development Agency of Chile (la Agencia Nacional de Investigación y Desarrollo); The National Fund for Scientific and Technological Development (Fondo Nacional de Desarrollo Científico y Tecnológico); Ministry of Health of Chile; Secretarías Regionales Ministeriales de Salud, Los Lagos (regional ministry of health); local health authorities.

Corresponding author: Constanza Martinez-Valdebenito, constanza.martinez.v@gmail.com.

[1]Laboratorio Clínico, Clínica Alemana, Facultad de Medicina Clinica Alemana, Universidad del Desarrollo, Santiago, Chile; [2]Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile; [3]Departamento de Enfermedades Infecciosas e Inmunología Pediátricas, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile; [4]Laboratorio de Infectología y Virología Molecular, Red Salud UC-Christus, Santiago, Chile; [5]Instituto de Medicina Preventiva Veterinaria and Center for Disease Surveillance and Evolution of Infectious Diseases, Facultad de Ciencias Veterinarias, Universidad Austral de Chile, Valdivia, Chile.

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. Thomas Weitzel, Constanza Martínez-Valdebenito, Katia Abarca, and Gerardo Acosta-Jamett report institutional support (including equipment and laboratory materials for diagnostic testing), travel support, and honoraria from the National Research and Development Agency of Chile (Agencia Nacional de Investigación y Desarrollo) and the National Fund for Scientific and Technological Development (Fondo Nacional de Desarrollo Científico y Tecnológico). No other potential conflicts of interest were disclosed.

References

1. Jiang J, Martínez-Valdebenito C, Weitzel T, et al. Development of a new genus-specific quantitative real-time PCR assay for the diagnosis of scrub typhus in South America. Front Med (Lausanne) 2022;9:831045. PMID:35573006 https://doi.org/10.3389/fmed.2022.831045
2. Kim IS, Walker DH. Scrub typhus [Chapter 51]. In: Guerrant RL, Walker DH, Weller PF, eds. Tropical infectious diseases: principles, pathogens and practice. 3rd ed. New York, NY: Elsevier Inc.; 2011:334–8.
3. Weitzel T, Dittrich S, López J, et al. Endemic scrub typhus in South America. N Engl J Med 2016;375:954–61. PMID:27602667 https://doi.org/10.1056/NEJMoa1603657
4. Abarca K, Martínez-Valdebenito C, Angulo J, et al. Molecular description of a novel *Orientia* species causing scrub typhus in Chile. Emerg Infect Dis 2020;26:2148–56. PMID:32818400 https://doi.org/10.3201/eid2609.200918
5. Silva-de la Fuente MC, Stekolnikov AA, Weitzel T, et al. Chigger mites (Acariformes: Trombiculidae) of Chiloé Island, Chile, with descriptions of two new species and new data on the genus *Herpetacarus.* J Med Entomol 2021;58:646–57. PMID:33300548 https://doi.org/10.1093/jme/tjaa258

Erratum

Vol. 72, No. Suppl-1

In the Supplement "Youth Risk Behavior Surveillance — United States, 2021," several errors occurred in the report "Alcohol and Other Substance Use Before and During the COVID-19 Pandemic Among High School Students — Youth Risk Behavior Survey, United States, 2021."

On page 84, in line 13 of the Abstract, the percentage should have read, "(**30%**)," and in line 14, the percentage should have read, "**35%**."

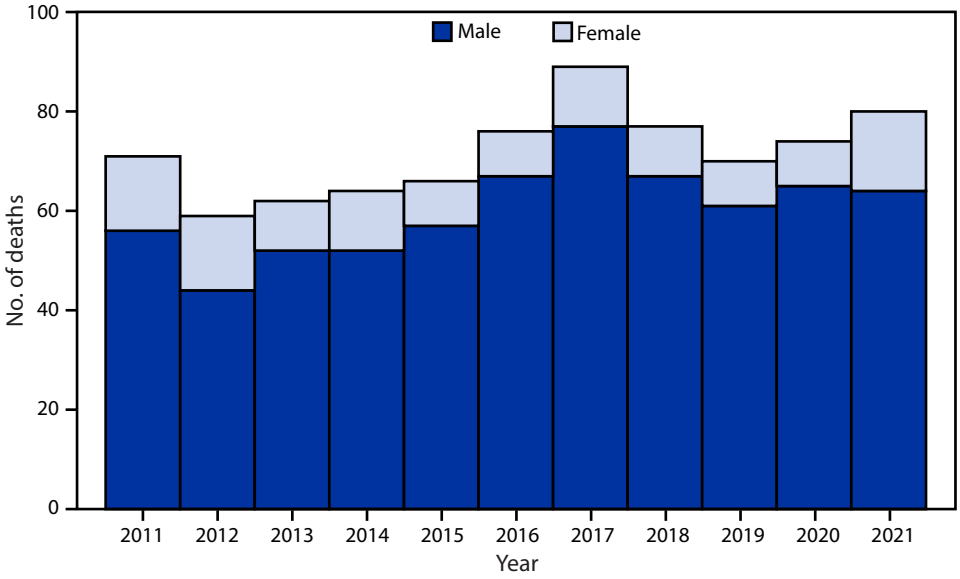
On page 87, the first sentence of the first footnote under Table 1 should have read, "* 2009: N = 16,410 respondents; 2011: N = 15,425 respondents; 2013: N = 13,583 respondents; 2015: N = 15,624 respondents; **2017: N = 14,765 respondents;** 2019: N = 13,677 respondents; 2021: N = 17,232 respondents."

On page 91, the first sentence of the first footnote under the Figure should have read, "* Previous 30 days before the survey; **n = 5,023** high school students who reported any current substance use."

QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Number of Deaths from Hornet, Wasp, and Bee Stings* Among Males and Females — National Vital Statistics System, United States, 2011–2021



* Deaths from hornet, wasp, and bee sting as underlying cause of death, were coded as X23, according to the *International Classification of Diseases, Tenth Revision*.

During 2011–2021, a total of 788 deaths from hornet, wasp, and bee stings occurred (an average of 72 deaths per year). The annual number of deaths ranged from 59 (2012) to 89 (2017). Overall, 84% of deaths occurred among males.

Source: National Center for Health Statistics, National Vital Statistics System, Mortality Data, 2011–2021. https://wonder.cdc.gov/Deaths-by-Underlying-Cause.html

Reported by: Jiaquan Xu, MD, jiaquanxu@cdc.gov.

The *Morbidity and Mortality Weekly Report (MMWR)* Series is prepared by the Centers for Disease Control and Prevention (CDC) and is available free of charge in electronic format. To receive an electronic copy each week, visit *MMWR* at *https://www.cdc.gov/mmwr/index.html*.

Readers who have difficulty accessing this PDF file may access the HTML file at https://www.cdc.gov/mmwr/index2023.html. Address all inquiries about the *MMWR* Series to Editor-in-Chief, *MMWR* Series, Mailstop V25-5, CDC, 1600 Clifton Rd., N.E., Atlanta, GA 30329-4027 or to mmwrq@cdc.gov.

ISSN: 0149-2195 (Print)