Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Impact of Rotavirus Vaccine Introduction and Vaccine Effectiveness in the Republic of Moldova

Stela Gheorghita,[1] Ludmila Birca,[2] Ala Donos,[3] Annemarie Wasley,[4] Ion Birca,[1] Radu Cojocaru,[1] Anatol Melnick,[1] Silviu Ciobanu,[5] Liudmila Mosina,[4] Margaret M. Cortese,[6] Umesh D. Parashar,[6] and Ben Lopman[6]

[1]National Center for Public Health, [2]Chisinau City Infectious Diseases Hospital for Children, and [3]Chisinau Municipal Hospital for Children, Republic of Moldova; [4]Vaccine-Preventable Diseases and Immunization, World Health Organization Regional Office for Europe, Copenhagen, Denmark; [5]World Health Organization Regional Office for Moldova, Chisinau; and [6]Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Background. The Republic of Moldova was the first low- to middle-income country in the World Health Organization European Region to introduce rotavirus vaccine (July 2012). We aimed to assess the impact of the rotavirus vaccine program and estimate vaccine effectiveness (VE).

Methods. Surveillance for rotavirus gastroenteritis was conducted in 2 hospitals in the capital city of Chisinau starting in September 2009. Monthly rotavirus admissions by age were examined before and after introduction of rotavirus vaccination using interrupted time-series analyses. We performed a case-control study of VE by comparing rotavirus case patients with test-negative controls.

Results. Coverage with at least 1 dose of vaccine increased from 35% in year 1 to 55% in year 2 for children <1 year of age. The percentage of hospital admissions positive for rotavirus fell from 45% in the prevaccine period to 25% (rate reduction, 36%; 95% confidence interval [CI], 26%–44%) and 14% (rate reduction, 67%; 95% CI, 48%–88%) in the first and second years after vaccine introduction, respectively, among children aged <5 years. Reductions were most pronounced among those aged <1 year. Significant reductions among cohorts too old to be vaccinated suggest indirect benefits. Two-dose VE was 79% (95% CI, 62%–88%) against rotavirus hospitalization and 84% (95% CI, 64%–93%) against moderate to severe rotavirus.

Conclusions. These results consistently point to profound direct and herd immunity impacts of the rotavirus vaccine program in young children in the Republic of Moldova. Vaccine coverage was modest in these early years following introduction, so there remains potential for further disease reductions.

Keywords. Moldova; rotavirus; surveillance; case-control; vaccine effectiveness.

Despite considerable progress, diarrheal disease remains the fourth most common cause of mortality and second most common cause of morbidity worldwide in children <5 years of age. Rotavirus is associated with approximately one-third of all severe diarrheal disease in young children, with recent estimates of annual rotavirus-associated mortality ranging from 453 000 (2008) to 197 000 (2010) and 173 000 (2011) [1–3]. Since 2009, the World Health Organization (WHO) has recommended that rotavirus vaccines be included in national immunization programs (NIPs) in every country and that introduction be considered a public health priority. Two rotavirus vaccines are licensed and used globally: monovalent Rotarix (RV1; Glaxo SmithKline) and pentavalent RotaTeq (RV5; Merck and Co). For both vaccines, clinical trials and postintroduction evaluations have indicated a gradient of performance with vaccine effectiveness (VE) ranging from approximately 70% to 100% in high- and upper-middle-income countries to approximately 50% to 70% in lower-income settings in Africa and Asia [4].

With financial support from Gavi, the Vaccine Alliance, rotavirus vaccination (RV1) was added to the Republic of Moldova's NIP in July 2012. Moldova was the first low- to middle-income country in the WHO European Region to introduce rotavirus vaccine. Vaccine is provided to all children through the NIP at no cost through primary healthcare centers and family doctor centers/offices. National guidelines stipulate that the first dose of RV1 be administered between 2 and 3.5 months of age and the second dose between 4 and 7 months of age.

Given that Moldova was the first country in the subregion to introduce rotavirus vaccination, we aimed to assess the impact of the program and to examine vaccine efficacy in the context of spectrum of VE from other settings. Specifically, we aimed to assess the impact of RV1 introduction on rotavirus-associated hospitalizations and to determine the effectiveness of RV1 in Moldova.

METHODS

Surveillance

The Republic of Moldova is a low- to middle-income country in the WHO European region and is a Newly Independent State of the former Soviet Union. The total population of Moldova is approximately 4 million, with an annual birth cohort of approximately 43 000.

Correspondence: B. Lopman, Centers for Disease Control and Prevention, 1600 Clifton Rd, NE, MS–A34, Atlanta, GA 30333 (iow4@cdc.gov).

Clinical Infectious Diseases® 2016;62(S2):S140–6

DOI: 10.1093/cid/civ1209

Sentinel surveillance for rotavirus gastroenteritis was conducted in 2 hospitals, both of which are in the capital city of Chisinau. The 100-bed Municipal Children's Infectious Diseases Hospital has conducted consistent surveillance since September 2009. Mainly, children aged 1–5 years are admitted to this hospital. To also capture infants aged <1 year, the 120-bed Municipal Children's Clinical Hospital No. 1 was added to the surveillance system from January 2012.

We conducted surveillance for children with acute diarrhea (defined as ≥3 loose stools in a 24-hour period and with onset <7 days prior to the hospital visit) per WHO-recommended protocol [5]. Surveillance was conducted 24 hours a day in the emergency department and inpatient units where we aimed to enroll all children <5 years of age who were admitted for diarrhea from the dates noted above for the 2 hospitals. Nurses and physicians in the wards were encouraged to notify the surveillance coordinator when treating children with diarrhea. The emergency department and hospital admission log was used to further identify any child with a chief complaint of vomiting or diarrhea. Bulk stool specimens were collected within 48 hours of admission. Specimens were stored at 2°C–8°C prior to transfer to the national laboratory on a weekly basis. Rotavirus testing was conducted using a commercially available enzyme immunoassay (ProSpecT; Oxoid, Cambridge, United Kingdom).

Data Collection

After written informed consent, basic demographic information was collected. For cases, we also gathered information on clinical characteristics, treatment, and course of illness through face-to-face interviews with parents of cases and controls during the hospital visit and review of medical records.

Vaccination history was obtained from records maintained at the healthcare centers or family doctor offices where the child was administered vaccine. Vaccination records at the clinic were identified on the basis of participant name, sex, and date of birth.

Vaccine Effectiveness Evaluation

We performed a case-control study of VE by comparing vaccination status of rotavirus case patients with controls. Case patients were identified by on-site study physicians and nurses from the surveillance network described above. All vaccine-eligible children (born on or after 1 May 2012) who were hospitalized after 1 October 2012 for acute gastroenteritis were enrolled and had their stool tested for rotavirus. Given the age restrictions of rotavirus vaccination in Moldova, we included only cases aged ≥6 months and excluded children who were administered a dose of rotavirus vaccine within 14 days of hospital admission. Controls were children with acute diarrhea subject to the same inclusion criteria as case patients but whose stool specimen tested negative for rotavirus.

Statistical Methods

Trends Analysis

Monthly rotavirus admissions by age were examined before (September 2009–July 2012) and after (year 1: August 2012–July 2013; year 2: August 2014–July 2013) introduction of rotavirus vaccination using an interrupted time-series analyses. A generalized linear model was fit to the time-series data, assuming that monthly counts of admissions were Poisson distributed. We adjusted for seasonality by including calendar month and "hospital" and accounted for total diarrhea admissions by considering the log-cases as the exposure. The rate ratio (RR) of rotavirus admissions in the vaccine era was calculated using an indicator variable for the year after rotavirus vaccine introduction, with prevaccine time as the referent. We investigated changes in rates by age groups (≤11 months, 12–23 months, 24–59 months) because vaccine coverage during the early years of an immunization program and disease rates vary substantially by age.

Case-Control Analysis

Our primary objective was to estimate VE of 1 or 2 doses of RV1 against rotavirus hospitalization. For secondary objectives, we also estimated VE stratified by age (6–11 months and 12–23 months) and doses of vaccine received (1 only and exactly 2). To investigate a potential gradient in protection by severity, we repeated all analyses for VE against moderate to severe rotavirus hospitalization, defined as hospital admission with rotavirus detected in stool by enzyme immunoassay and with a clinical severity score of ≥10 on a modified 20-point Vesikari scoring scale [6].

To estimate VE, we fit unconditional logistic regression models to calculate odds ratios of vaccination by rotavirus case patient status, with associated 95% confidence intervals (CIs) [7]. All models controlled for age and hospital. VE was calculated as (1 − odds ratio × 100%). Statistical significance was designated as a P value <.05. Analyses were done with Stata software version 13.0 (StataCorp, College Station, Texas).

RESULTS

Coverage with at least 1 dose of RV1 among rotavirus-negative controls increased from negligible levels prior to vaccine introduction (July 2012) to 20% in year 1 and 40% in year 2 postvaccination among children aged <5 years (Table 1). In children aged <1 year, RV1 coverage increased from 35% in year 1, reaching only 55% in year 2. Vaccination was generally timely, with the first dose administered between the eighth and 15th weeks of life for 88.3% of vaccinated children and the second dose administered between the 16th and 35th weeks of life for 96.1% of vaccinated children (Figure 1).

Rotavirus Trends

Rotavirus-associated hospitalizations decreased following vaccine introduction (Table 1; Figure 2). In the first and second

Table 1. Trends in Rotavirus Vaccine Coverage and Rotavirus Positivity and Relative Risk of Hospitalization for Rotavirus Gastroenteritis by Age Among Children <5 Years of Age, Moldova, September 2009–July 2014

Age Group	Prevaccine (Sept 2009–July 2012)	Year 1 Postvaccine (Aug 2012–July 2013)	Year 2 Postvaccine (Aug 2013–July 2014)
≤11 mo			
Vaccine coverage[a], No. (%)	4/626 (<1)	179/507 (35)	236/427 (55)
RV^+/No.[b] (%)	247/873 (28)	83/590 (14)	31/458 (6)
Rate reduction[c], % (95% CI)	1	49 (34–64)	73 (53–84)
12–23 mo			
Vaccine coverage[a], No. (%)	3/799 (<1)	9/216 (4)	125/307 (41)
RV^+/No.[b] (%)	725/1524 (48)	111/327 (33)	43/350 (13)
Rate reduction[c], % (95% CI)	1	25 (14–35)	75 (55–86)
24–59 mo			
Vaccine coverage[a], No. (%)	3/658 (<1)	2/230 (<1)	38/265 (14)
RV^+/No.[b] (%)	732/1390 (53)	116/346 (33)	84/349 (22)
Rate reduction[c], % (95% CI)	1	32 (22–41)	55 (30–72)
Total (<5 y)			
Vaccine coverage[a], No. (%)	10/2083 (<1)	190/953 (20)	399/999 (40)
RV^+/No.[b] (%)	1704/3787 (45)	310/1263 (25)	158/1157 (14)
Rate reduction[c], % (95% CI)	1	36 (36–44)	67 (48–87)

Abbreviations: CI, confidence interval; RV, rotavirus.

[a] Coverage of 1 or more doses among rotavirus-negative children (ie, controls) hospitalized for acute gastroenteritis (AGE).

[b] No. = total AGE patients tested by enzyme immunoassay.

[c] Compared to prevaccine period, adjusting for hospital and calendar month.

years after vaccine introduction, the percentage of hospital admissions positive for rotavirus fell from 45% in the prevaccine period to 25% (RR, 0.64 [95% CI, .56–.74]) and 14% (RR, 0.33 [95% CI, .22–.52]), respectively, among those aged <5 years. These patterns were most pronounced among children aged <1 year, among whom rotavirus prevalence fell from 28% in the prevaccine period to 14% (rate reduction, 79% [95% CI, 34%–64%]) and 6% (rate reduction, 73% [95% CI, 53%–84%]) in the first and second years postvaccination, respectively. Rotavirus prevalence also decreased among children aged 12–23 months, from 48% prevaccine to 33% (rate reduction, 25% [95% CI, 14%–35%]) and 13% (rate reduction, 75% [95% CI,

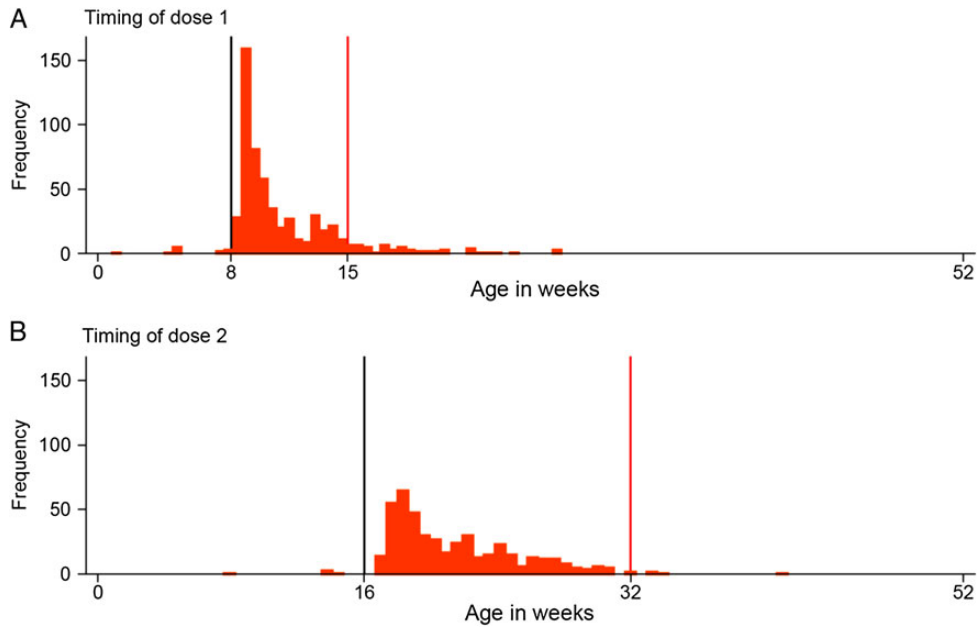

Figure 1. Age in weeks of receipt of dose 1 (*A*) and dose 2 (*B*) of monovalent rotavirus vaccine, Moldova, August 2012–July 2014.

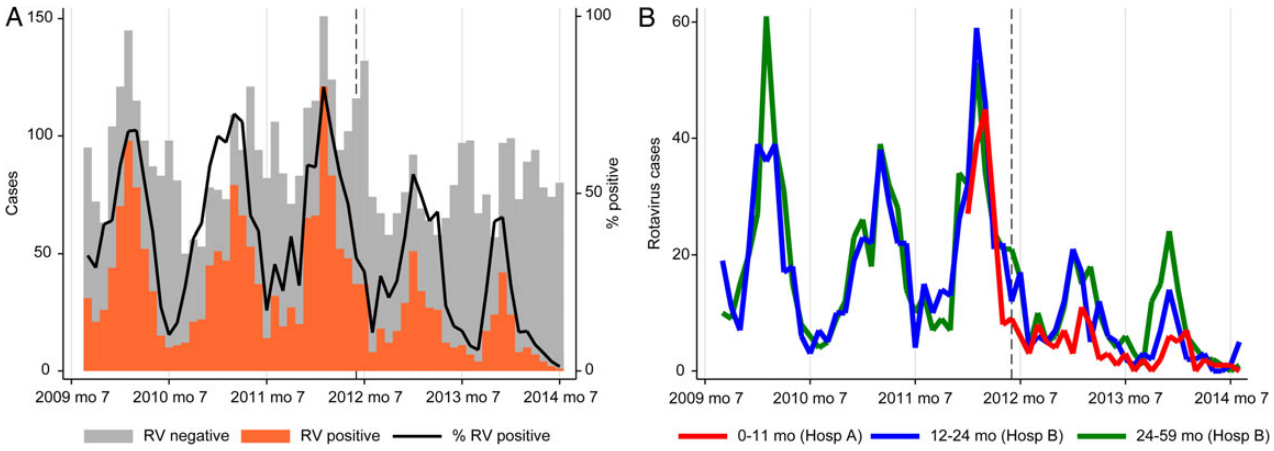

Figure 2. *A*, Rotavirus–positive and rotavirus-negative hospital admissions among children <5 years of age (includes only data from the Municipal Children's Infectious Diseases Hospital, which conducted consistent surveillance since September 2009), Moldova, September 2009–July 2014. *B*, Rotavirus-positive hospital admissions by age, Moldova, September 2009–July 2014. Abbreviation: RV, rotavirus.

55%–86%]) in the first and second years postvaccination, respectively, and decreased among children aged 24–59 months, from 53% prevaccine to 33% (rate reduction, 32% [95% CI, 22%–41%]) and 22% (rate reduction, 55% [95% CI, 30%–72%]) in the first and second years postvaccination, respectively.

Notably, significant reductions occurred among cohorts who were too old to be vaccinated (age 12–59 months in year 1, and age 24–59 months in year 2). In fact, the level of reduction (ie, 1 – RR) among all age groups in all postvaccination periods was greater than vaccine coverage among controls, suggestive of indirect benefits (Figure 3). In the prevaccine period and in year 1 postvaccination, the median age of rotavirus cases was 20 months (interquartile range [IQR], 14–31 and 13–22 months, respectively), whereas in year 2 the median age was 23 months (IQR, 14–36 months) in the Municipal Children's Infectious Diseases Hospital, which consistently conducted surveillance in 1- to 4-year-olds.

Vaccine Effectiveness From Case-Control Study

A total of 1433 children were enrolled in the case-control study, of whom 995 (69%) were aged 6–23 months; 957 of these 995 children submitted a stool sample (96%), 857 of whom tested negative (89.5%; controls) and 100 tested positive (10.5%; cases) for rotavirus, among whom 67 (67%) were moderate to severe cases. Of these remaining eligible children, documented vaccine status was available for 914 (96%). Controls and cases were similar in terms of age, proportion female, documented vaccination status, and residence in Chisinau capital district; controls had significantly lower severity score than cases (8.8 and 10.4, respectively, $P < .001$; Table 2).

Fifty-two percent of controls (422/819), 25% of cases (20/95), and 16% (12/62) of moderate to severe cases received at least 1 dose of vaccine. Overall, VE with 1 or more doses was 75% (95%

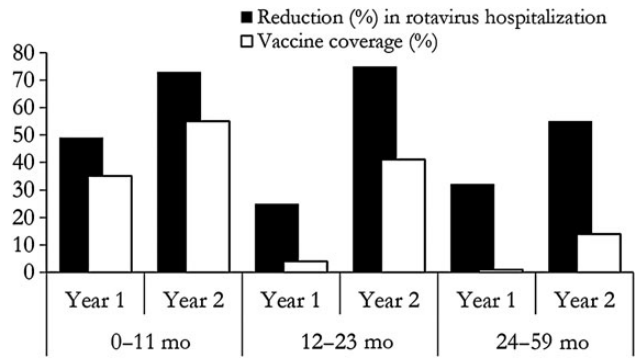

Figure 3. Percentage reduction in rotavirus hospitalizations and any-dose vaccine coverage in the first and second years following vaccine introduction, by age, Moldova, August 2012–July 2014.

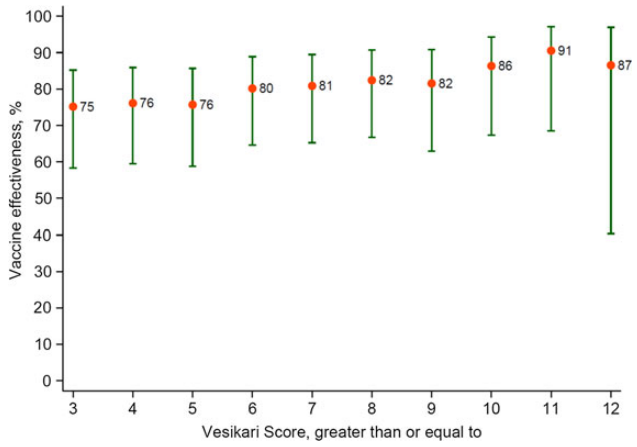

Figure 4. Vaccine effectiveness (VE) percent estimates against rotavirus hospitalization by severity score, Moldova, August 2012–July 2014. All VE estimates control for hospital and age group.

Table 2. Sociodemographic and Clinical Characteristics of Cases and Controls

Characteristic	Cases (n = 100)	Controls (n = 852)	*P* Value
Age, mo, mean (SD)	11.6 (4.9)	11.6 (4.9)	.27
Female sex, No. (%)	49 (49)	364 (43)	.23
Documented vaccination history, No. (%)	95 (95)	819 (96)	.59
Residence in Chisinau district, No. (%)	83 (84)	683 (80)	.94
Vesikari severity score[a], mean (SD)	10.4 (2.4)	8.8 (2.4)	<.001

Abbreviation: SD, standard deviation.

[a] Modified Vesikari score is a sum of duration of diarrhea (0–3 points); maximum number of episodes of diarrhea in a 24-hour period (0–3 points); duration of vomiting (0–3 points); maximum number of episodes of vomiting in a 24-hour period (0–3 points); maximum temperature (0–3 points); level of dehydration (0–4 points); and whether the child was hospitalized (2 points).

CI, 58%–85%) against rotavirus hospitalization and 82% (95% CI, 63%–91%) against moderate to severe rotavirus hospitalization (Table 3). VE was higher for each incrementally higher severity score (Figure 4).

VE for a full 2-dose course against rotavirus hospitalization (79% [95% CI, 62%–88%]) appeared greater than a single dose (60% [95% CI, 4%–85%]), though this difference was not of statistical significance ($P = .39$). VE against rotavirus hospitalization in the first year of life (84% [95% CI, 67%–92%]) appeared to be higher than in the second year of life (46% [95% CI, −16% to 75%]), although this difference was not of statistical significance ($P = .23$).

For all analyses, there was a nonsignificantly higher VE against moderate to severe rotavirus compared to the VE against rotavirus hospitalization. For example, VE for a full 2-dose course against moderate to severe rotavirus hospitalization was 84% (95% CI, 64%–93%) compared with 79% (95% CI, 62%–88%) against all rotavirus hospitalizations.

DISCUSSION

Moldova was the first WHO European Region country to introduce rotavirus vaccination into its routine childhood immunization schedule. These results consistently point to a profound impact of the program on rotavirus disease in young children in Chisinau, Moldova. VE of 2 doses was fairly high at 79% against rotavirus hospitalization and 84% against hospitalization for severe disease. Overall, rotavirus hospitalizations decreased by two-thirds by the second year of the program in a pattern consistent with vaccine impact. Decreases were greatest among vaccinated cohorts—that is, children <1 year of age in the first year and <2 years of age in the second year following vaccine implementation. In addition, there were clear decreases in rotavirus hospitalizations for all children <5 years of age, including unvaccinated cohorts, strongly suggestive of indirect protection resulting from infant immunization.

A strength of this study is the combination of surveillance and case-control data, allowing us to examine both trends and vaccine protection. We had 3 years of surveillance data prior to vaccine introduction. Using this surveillance infrastructure, we transitioned to perform a case-control study, principally by adding the collection of vaccination history data from all eligible enrolled subjects. Compared to community or hospital controls, test-negative controls have the advantages of being comparatively straightforward to recruit, having similar care-seeking behavior as cases, and having less likelihood of bias in ascertainment of vaccination status as the study team remains blinded to the subjects' case/control status.

There are some limits to the generalizability of these results. First, our surveillance was restricted to the capital district of Chisinau, where approximately one-quarter of the population lives, so may not be representative of more rural parts of Moldova. Second, we had limited data on hospitalization trends in children aged <1 year. We added a second surveillance site at a children's hospital in January 2012 to have sufficient numbers of subjects to evaluate VE in those aged <1 year, but had limited historic data on trends in this age group. Third, the threshold for hospital admission in Moldova and some other Newly Independent States of the former Soviet Union may be lower, such that mild cases are admitted who might receive outpatient care in other healthcare systems. For this reason, we analyzed vaccine efficacy for all rotavirus hospitalizations and moderate to

Table 3. Monovalent Rotavirus Vaccine Effectiveness Overall, by Number of Doses and Age Against All Rotavirus Hospitalization and Moderate to Severe Rotavirus Hospitalization

		All Rotavirus Hospitalizations			Moderate to Severe Rotavirus Hospitalizations		
Doses and Age	Controls Vaccinated/No. (%)	Vaccinated/No. (%)	VE, % (95% CI)	*P* Value	Vaccinated/No. (%)	VE, % (95% CI)	*P* Value
Overall[a]	422/819 (52)	20/95 (25)	75 (58–85)	<.001	10/62 (16)	82 (63–91)	<.001
1 dose	51/448 (11)	4/79 (5)	60 (4–85)	.04	2/54 (7)	71 (2–92)	.046
2 doses	348/745 (47)	14/89 (16)	79 (62–88)	<.001	7/59 (12)	84 (64–93)	<.001
Age 6–11 mo[a]	274/485 (56)	10/57 (18)	84 (67–92)	<.001	3/31 (10)	92 (72–98)	<.001
Age 12–23 mo[a]	136/316 (43)	10/36 (28)	46 (−16 to 75)	.11	7/29 (24)	67 (−3 to 83)	.060

All analyses control for age and hospital as a categorical variable and were restricted to children with verified vaccination status.

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

[a] For 1 or more doses of monovalent rotavirus vaccine.

severe cases separately. Indeed, we found a higher VE of 82% against severe disease. This VE is in line with estimates of protection against hospitalization and severe disease in middle- to high-income settings [8]. The lower VE in Moldova against all rotavirus hospitalizations is consistent with the notion that less severe cases are hospitalized in this country and that rotavirus vaccines are most effective against severe disease [8].

It is well established that rotavirus vaccines are less effective in low-income settings than in higher-income settings; however, the specific reasons underlying this phenomenon are unclear. Based on income, Moldova ranks below both El Salvador, Brazil, Bolivia, and Colombia, but has a higher point estimate of VE (82%) than any of these Latin American nations (76%, 40%–77%, 72%, and −2%, respectively) [9–13]. Moldova's 2-dose RV1 VE estimate, especially against severe disease at 84% (95% CI, 65%–93%), is highly consistent with vaccine efficacy estimates from other low-mortality countries (in WHO mortality strata A and B) where VE is 85% (95% CI, 80%–88%) based on pooled analysis of 8 trials including >32 000 participants [8].

With 55% of the birth cohort vaccinated by the second post-vaccination year and overall VE of 75%, the maximum direct effect of vaccination would be a 41% reduction in disease rates (55% × 75%). However, we observed an average reduction over the 2-year period of 61% among children aged <1 year and 52% in those aged <5 years. Similarly, in the United States, in the second year of vaccine impact, expected reductions based on direct effects alone were 49% compared with observed reductions up to 89%. Countries including the United States, El Salvador, Australia, Austria, and Belgium have all observed reductions in rotavirus hospitalizations in older, unvaccinated age groups [14–17]. In most settings, these reductions have been noted for children aged 24–59 months, but in Australia and the United States there are data to suggest that these indirect benefits extend to older children and adults [14, 16, 18]. Indirect protection from rotavirus vaccination is a result of interruption of transmission by reducing the incidence among infants, and thereby reducing exposure of unvaccinated and/or older age groups to infected infants.

In summary, we have observed a clear impact of the introduction of rotavirus vaccination into the infant immunization program of Moldova, and have measured robust VE. However, with modest vaccine coverage (only reaching 55% in children aged <1 year), there is potential for further reductions in disease. This analysis has implications for Moldova as it is set to "graduate out" of Gavi support eligibility and will increasingly be responsible for financing of its national vaccination program. These early impact data clearly argue for sustained use of rotavirus vaccine, with further benefits possible with improved coverage. These data should be encouraging for other countries in the region considering introducing rotavirus vaccine into their national programs. We recommend continued surveillance for rotavirus gastroenteritis in Moldovan hospitals to monitor vaccine uptake and to assess the medium- and long-term benefits of rotavirus vaccination.

Notes

Acknowledgments. The authors thank Dovile Videbaek at the World Health Organization Regional Office for Europe and Drs Olga Burduniuc, Tatiana Juravlev, and Maria Ganea at the Municipal Children's Infectious Diseases Hospital and Children's Clinical Hospital No. 1 in Chisinau, Moldova.

Disclaimer. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). The views expressed by the authors do not necessarily reflect the views of PATH, the CDC Foundation, the Bill and Melinda Gates Foundation, or GAVI, the Vaccine Alliance.

Financial support. This work was supported by Gavi, the Vaccine Alliance.

Supplement sponsorship. This article appears as part of the supplement "Health Benefits of Rotavirus Vaccination in Developing Countries," sponsored by PATH and the CDC Foundation through grants from the Bill and Melinda Gates Foundation and GAVI, the Vaccine Alliance.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Tate JE, Burton AH, Boschi-Pinto C, et al. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis **2012**; 12:136–41.
2. Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet **2012**; 379:2151–61.
3. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet **2015**; 385:430–40.
4. Yen C, Tate JE, Hyde TB, et al. Rotavirus vaccines: current status and future considerations. Hum Vaccin Immunother **2014**; 10:1436–48.
5. World Health Organization. Generic protocols for (i) hospital-based surveillance to estimate the burden of rotavirus gastroenteritis in children and (ii) a community-based survey on utilization of health care services for gastroenteritis in children. Geneva, Switzerland. **2002**. Available at: http://apps.who.int/iris/bitstream/10665/67743/1/WHO_V-B_02.15_eng.pdf.
6. Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. Scand J Infect Dis **1990**; 22:259–67.
7. Hosmer DW, Lemeshow S. Applied logistic regression. 2nd ed. New York: Wiley, **2000**.
8. Soares-Weiser K, Maclehose H, Bergman H, et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev **2012**; 11: CD008521.
9. de Palma O, Cruz L, Ramos H, et al. Effectiveness of rotavirus vaccination against childhood diarrhoea in El Salvador: case-control study. BMJ **2010**; 340: c2825.
10. Justino MC, Linhares AC, Lanzieri TM, et al. Effectiveness of the monovalent G1P[8] human rotavirus vaccine against hospitalization for severe G2P[4] rotavirus gastroenteritis in Belem, Brazil. Pediatr Infect Dis J **2011**; 30: 396–401.
11. Patel MM, Patzi M, Pastor D, et al. Effectiveness of monovalent rotavirus vaccine in Bolivia: case-control study. BMJ **2013**; 346:f3726.
12. Ichihara MY, Rodrigues LC, Teles Santos CA, et al. Effectiveness of rotavirus vaccine against hospitalized rotavirus diarrhea: a case-control study. Vaccine **2014**; 32:2740–7.
13. Cotes-Cantillo K, Paternina-Caicedo A, Coronell-Rodriguez W, et al. Effectiveness of the monovalent rotavirus vaccine in Colombia: a case-control study. Vaccine **2014**; 32:3035–40.
14. Gastanaduy PA, Curns AT, Parashar UD, Lopman BA. Gastroenteritis hospitalizations in older children and adults in the United States before and after implementation of infant rotavirus vaccination. JAMA **2013**; 310:851–3.

15. Yen C, Armero Guardado JA, Alberto P, et al. Decline in rotavirus hospitalizations and health care visits for childhood diarrhea following rotavirus vaccination in El Salvador. Pediatr Infect Dis J **2011**; 30(1 suppl):S6–10.
16. Buttery JP, Lambert SB, Grimwood K, et al. Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's national childhood vaccine schedule. Pediatr Infect Dis J **2011**; 30(1 suppl):S25–9.
17. Paulke-Korinek M, Kundi M, Rendi-Wagner P, et al. Herd immunity after two years of the universal mass vaccination program against rotavirus gastroenteritis in Austria. Vaccine **2011**; 29:2791–6.
18. Standaert B, Gomez JA, Raes M, Debrus S, Velazquez FR, Postma MJ. Impact of rotavirus vaccination on hospitalisations in Belgium: comparing model predictions with observed data. PLoS One **2013**; 8:e53864.