Public health impact of accelerated immunization against rotavirus infection among children aged less than 6 months in the United States

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We developed a cohort model to evaluate the expected public health impact of accelerated regimens for immunization against rotavirus gastroenteritis (RVGE). Alternative strategies for vaccination with the pentavalent human-bovine reassortant vaccine, *Rotateq*® (RV5, Merck) and the oral live attenuated human rotavirus vaccine, *Rotarix*® (RV1, GlaxoSmithKline Vaccines) were considered, including acceleration of the 1st dose only (by 2 weeks) as well as acceleration of the 1st (by 2 weeks) and subsequent doses (by up to 10 weeks). Assuming vaccine coverage levels consistent with current US clinical practice, accelerated regimens would be expected to reduce annual numbers of RVGE-related hospitalizations by 300–400, emergency department visits by 3000–4000, and outpatient visits by 3000–4000 (i.e., by 9–14%) among US children aged <6 months. Accordingly, accelerating the immunization of children against RVGE may yield substantive reductions in the number of RV-related encounters in US clinical practice.

Introduction

Two rotavirus (RV) vaccines—*Rotateq*® (RV5, Merck), a 3-dose pentavalent human-bovine RV based vaccine, and *Rotarix*® (RV1, GlaxoSmithKline Vaccines), a 2-dose monovalent human RV based vaccine—are currently available in the US and are recommended by the Advisory Committee on Immunization Practice (ACIP) for routine use among US infants.[1] Both vaccines have been proven to be safe and highly efficacious against severe rotavirus gastroenteritis (RVGE).[2-4] The widespread use of rotavirus vaccine in the US has resulted in substantial reductions in RV-associated disease among those vaccinated as well as those not vaccinated (i.e., via a so-called "herd effect" or "indirect effect").[5]

According to ACIP recommendations, RV5 is to be administered at 2, 4, and 6 mo of age, while RV1 at 2 and 4 mo of age; all doses are to be completed before 32 wk of age.[1] According to the respective prescribing information, however, the initial dose of each vaccine may be administered as early as 6 wk and the interval separating doses may be as short as 4 wk.[6,7] It thus may be possible to accelerate administration of the 1st dose by up to 2 wk and subsequent doses by up to 10 wk—relative to ACIP recommendations—in clinical practice, which would confer earlier protection of children against RV infection.

The impact of accelerating the 1st dose of RV vaccine was evaluated in a recent modeling exercise by Halvorson and colleagues.[8] In their study, Halvorson and colleagues reported a substantial reduction in RV-related hospitalizations by accelerating the administration of the 1st dose of RV vaccine by 2 wk. We sought to expand on these findings by considering alternative strategies for accelerated vaccination and additional measures of disease burden including RV-related emergency department (ED) visits and outpatient visits.

Results

Vaccination per US clinical practice

Assuming use of RV5 and RV1 consistent with current US clinical practice, the expected annual numbers of RVGE-related hospitalizations, ED visits, and outpatient visits among children aged <6 mo with the Base Case Schedule would total 2718, 33409, and 29473, respectively. With the Accelerated 1st Dose Schedule, the expected annual numbers of hospitalizations, ED visits, and outpatient visits would be reduced by 10%, 9%, and 9%, respectively. With the Accelerated 1st/2nd Dose Schedule, corresponding expected reductions would be 12%, 10%, and 10%. With the Accelerated 1st/2nd/3rd Dose Schedule, corresponding expected reductions would be 14%, 13%, and 13%

Table 1. Expected annual numbers of medically-attended episodes of RVGE among infants aged 0 to <6 mo with use of RV1 and RV5

Scenario	Vaccination schedule	Hospitalizations		ED visits		Outpatient visits	
		Number	Percentage reduction from Base Case	Number	Percentage reduction from Base Case	Number	Percentage reduction from Base Case
US clinical practice	Base Case Schedule[a]	2718		33 409		29 473	
	Accelerated						
	1st Dose Schedule[b,c]	2444	10.1%	30 364	9.1%	26 786	9.1%
	1st/2nd Dose Schedule[d,e]	2394	11.9%	30 137	9.8%	26 586	9.8%
	1st/2nd/3rd Dose Schedule[d,f]	2332	14.2%	29 147	12.8%	25 713	12.8%
Full vaccination	Base Case Schedule[a]	1994		25 487		22 484	
	Accelerated						
	1st Dose Schedule[b,c]	1619	18.8%	21 327	16.3%	18 814	16.3%
	1st/2nd Dose Schedule[d,e]	1545	22.5%	20 985	17.7%	18 513	17.7%
	1st/2nd/3rd Dose Schedule[d,f]	1433	28.1%	19 206	24.6%	16 943	24.6%

[a]RV1: dose 1 at 8 wk, dose 2 at 16 wk; RV5: dose 1 at 8 wk, dose 2 at 16 wk, dose 3 at 24 wk; [b]RV1: dose 1 at 6 wk, dose 2 at 16 wk; [c]RV5: dose 1 at 6 wk, dose 2 at 16 wk, dose 3 at 24 wk; [d]RV1: dose 1 at 6 wk, dose 2 at 10 wk; [e]RV5: dose 1 at 6 wk, dose 2 at 10 wk, dose 3 at 24 wk; [f]RV5: dose 1 at 6 wk, dose 2 at 10 wk, dose 3 at 14 wk;

(**Table 1**). Results assuming use of RV5 only and, alternatively, RV1 only are set forth in **Table 2**.

Full vaccination

Assuming all children were fully vaccinated with RV5 (92%) or RV1 (8%), the expected annual numbers of RVGE-related hospitalizations, ED visits, and outpatient visits among children aged <6 mo with the Base Case Schedule would total 1994, 25 487, and 22 484, respectively. With the Accelerated 1st Dose Schedule, the expected annual numbers of hospitalizations, ED visits, and outpatient visits would be reduced by 19%, 16%, and 16%, respectively. With the Accelerated 1st/2nd Dose Schedule, corresponding expected reductions would be 23%, 18%, and 18%. With the Accelerated 1st/2nd/3rd Dose Schedule, corresponding reductions would be 28%, 25%, and 25%.

Sensitivity analyses

Model results were insensitive to reasonable variation in the risks of RVGE-related encounters and indirect effects of vaccination (**Tables 1 and 2**; **Supplemental Material**). When vaccine effectiveness was set equal to lower-bound values, and assuming 100% compliance with vaccination, the reduction in RVGE-related encounters with the Accelerated Schedules was lower by 6–10% (i.e., percentage points).

Discussion

We developed a model depicting annual rates of medically-attended RVGE cases among children less than 6 mo of age to evaluate the expected impact of accelerated RV vaccination schedules. The benefit of accelerated vaccination was assumed to be mediated entirely through the earlier protection of children against RV infection, and was assumed to have a similar risk-benefit profile to vaccination under the Base Case Schedule (i.e., per ACIP recommendations).

Our results suggest that accelerated RV vaccination would reduce annual numbers of RVGE-related hospitalizations by 300–400, ED visits by 3000–4000, and outpatient visits by 3000–4000 in US clinical practice, assuming not all children will be vaccinated and depending on the precise vaccination schedule. We note that these findings were generated using the highest levels of herd effects reported in the study by Cortes et al.[5] If, in the real-world, herd effects were lower, the absolute benefits of accelerated vaccination would be correspondingly higher.

Importantly, for the scenario (accelerated 1st dose only) and the measure (RVGE hospitalizations) that are common between our study and the Halvorson et al. study,[8] our model yielded substantially lower reductions (274 vs. 737–2210 [depending on vaccine coverage and efficacy]). While differences between studies in assumed levels of RVGE hospitalizations, vaccine coverage, and vaccine effectiveness may explain some of this discrepancy, we believe the primary reason for the discrepancy is the difference in our (vs. their) interpretation and use of the underlying RVGE hospitalization rate for children aged less than 3 mo (Staat et al.).[9] In the study by Staat et al., hospitalization rates were calculated for each study year (July–June) by dividing the total number of children hospitalized with RVGE (based on the alternative

Table 2. Expected annual numbers of medically-attended episodes of RVGE among infants aged 0 to <6 mo with use of only RV1 and, alternatively, only RV5

Scenario	Vaccination schedule	Hospitalizations		ED visits		Outpatient visits	
		Number	Percentage reduction from Base Case	Number	Percentage reduction from Base Case	Number	Percentage reduction from Base Case
Vaccination with RV1							
US clinical practice	Base Case Schedule[a]	2544		32362		28549	
	Accelerated						
	1st Dose Schedule[b]	2245	11.8%	29217	9.7%	25775	9.7%
	1st/2nd Dose Schedule[d]	2173	14.6%	28450	12.1%	25098	12.1%
Full vaccination	Base Case Schedule[a]	1749		23994		21167	
	Accelerated						
	1st Dose Schedule[b]	1341	23.3%	19697	17.9%	17377	17.9%
	1st/2nd Dose Schedule[d]	1224	30.0%	18463	23.1%	16288	23.1%
Vaccination with RV5							
US clinical practice	Base Case Schedule[a]	2734		33503		29556	
	Accelerated						
	1st Dose Schedule[c]	2462	10.0%	30467	9.1%	26878	9.1%
	1st/2nd Dose Schedule[e]	2414	11.7%	30289	9.6%	26721	9.6%
	1st/2nd/3rd Dose Schedule[f]	2346	14.2%	29210	12.8%	25768	12.8%
Full vaccination	Base Case Schedule[a]	2016		25622		22603	
	Accelerated						
	1st Dose Schedule[c]	1644	18.4%	21474	16.2%	18944	16.2%
	1st/2nd Dose Schedule[e]	1574	21.9%	21213	17.2%	18714	17.2%
	1st/2nd/3rd Dose Schedule[f]	1452	28.0%	19273	24.8%	17002	24.8%

[a]RV1: dose 1 at 8 wk, dose 2 at 16 wk; RV5: dose 1 at 8 wk, dose 2 at 16 wk, dose 3 at 24 wk; [b]RV1: dose 1 at 6 wk, dose 2 at 16 wk; [c]RV5: dose 1 at 6 wk, dose 2 at 16 wk, dose 3 at 24 wk; [d]RV1: dose 1 at 6 wk, dose 2 at 10 wk; [e]RV5: dose 1 at 6 wk, dose 2 at 10 wk, dose 3 at 24 wk; [f]RV5: dose 1 at 6 wk, dose 2 at 10 wk, dose 3 at 14 wk;

ascertainment methods) in a given age cohort during that study year by the total number of children in that age cohort (based on intercensal estimates) during that study year. Accordingly, we assumed that the hospitalization rate of 52 per 10 000 children aged less than 3 mo reported by Staat et al. reflected the burden among all children in this age group over a 12-mo period.[9] On the other hand, it appears that the Halvorson study assumed that the hospitalization rate corresponded to a 3-mo period (i.e., from birth up to 12 wk of age). We believe, therefore, that Halvorson et al. may have overestimated the number of hospitalizations and corresponding reductions with accelerated vaccination.[8] To further support our interpretation and use of the reported hospitalization rate, we note that the overall rate from Staat et al. (26.9 per 10 000 children aged less than 3 y) roughly corresponds to the overall rate from Payne et al. (22.5 per 10 000 children aged less than 3 y), and the latter was used by Payne and colleagues

to estimate the total number of hospitalizations in the US on an annual basis.[9,10]

We note several limitations of our study. First, estimates of vaccine effectiveness were obtained from a previously published cost-effectiveness study,[11] which derived values using efficacy data from pivotal Phase III clinical trials of RV5 and RV1. Evidence from clinical trials, however, may not be reflective of real-world clinical practice as patients and their care may vary greatly between these settings. Although some published evidence exists regarding the effectiveness of RV5 in clinical practice,[12] comparable data on the effectiveness of RV1 are only beginning to accumulate and the evidence currently available for use is limited. In addition, we assumed no delay in infants' immune response to vaccination, irrespective of the schedule for administration. Second, since robust head-to-head clinical studies of RV5 and RV1 are not currently available, and thus the

Table 3. Model parameter values - rates of medically-attended RVGE among infants aged 0 to <6 mo

Variables	Category	Parameter	Value	Source
Rates of RVGE requiring medical care in pre-vaccination era (annual, per 100 children)	Outpatient visit	Aged 0 to <3 mo	4.59	[8, 9]
		Aged 3 to <6 mo	2.66	
	Emergency department visit	Aged 0 to <3 mo	4.43	[8, 9]
		Aged 3 to <6 mo	2.57	
	Hospitalization	Aged 0 to <3 mo	0.52	[8]
		Aged 3 to <6 mo	0.30	
Reduction in RVGE rates from indirect effects of routine vaccination, %	Outpatient visit	-	37.0	[10]
	Emergency department Visit	-	25.5	
	Hospitalization	-	46.0	
Rates of RVGE requiring medical care in post-vaccination era (per 100 children)	Outpatient visit	Aged 0 to <3 mo	2.89	Derived
		Aged 3 to <6 mo	1.68	
	Emergency department visit	Aged 0 to <3 mo	3.30	
		Aged 3 to <6 mo	1.91	
	Hospitalization	Aged 0 to <3 mo	0.28	
		Aged 3 to <6 mo	0.16	
RV5 effectiveness, %	Outpatient visit	Dose 1 to 2	78.0	[11]
		Dose 2 to 3	79.9	
		Dose 3 to end of 1st yr	92.5	
	Emergency department visit	Dose 1 to 2	78.0	
		Dose 2 to 3	79.9	
		Dose 3 to end of 1st yr	92.5	
	Hospitalization	Dose 1 to 2	82.0	
		Dose 2 to 3	88.0	
		Dose 3 to end of 1st yr	97.3	
RV1 effectiveness, %	Outpatient visit	Dose 1 to 2	80.8	[11]
		Dose 2 to end of 1st yr	89.8	
	Emergency department visit	Dose 1 to 2	80.8	
		Dose 2 to end of 1st yr	89.8	
	Hospitalization	Dose 1 to 2	90.0	
		Dose 2 to end of 1st yr	100.0	

comparative effectiveness of the 2 vaccines is unknown, caution should be exercised in interpreting the results of analyses assuming use of each vaccine separately. To the extent that effectiveness is comparable between vaccines beginning with dose 1, the projected benefit of accelerated vaccination would be similar for RV5 and RV1. Third, while we believe surveillance data provide the most accurate estimates of the underlying burden of RVGE, rates of RVGE-related ED visits were based on data from only 3 sites during a single season, and rates of RVGE-related hospitalizations were based on surveillance data from only 1 site over a multi-year period. Moreover, because surveillance data were not available for RVGE-related outpatient visits, estimates that were calculated using an "indirect method" (the accuracy of which is unknown) were employed in our analyses. Fourth, although

the RV season typically spans only 4 to 6 mo in a calendar year,[13] rates of RV-related encounters reported in various studies—that were used as sources for our model—were annualized. Thus, our estimates of reductions in rates of hospitalizations, ED and outpatient visits due to RV have been expressed on a yearly basis. Fifth, we note that our analyses did not consider additional healthcare encounters that might result from accelerated schedules for administration of vaccine (i.e., because of the need for visits outside of the currently recommended schedule for vaccination or increased risk of vaccine-associated adverse events). We also note, however, as pointed out by Halvorson and colleagues, all of the vaccines that are currently recommended for administration at 8 wk of age could be given as early as 6 wk of age, and an extra healthcare encounter could be

Table 4. Vaccine coverage rates

	US clinical practice	Full vaccination
No vaccination	27%	0%
Vaccination (≥1 doses)	73%	100%
RV5	67%	92%
1 dose	5%	0%
2 doses	11%	0%
3 doses	51%	92%
RV1	6%	8%
1 dose	1%	0%
2 doses	5%	8%

avoided by accelerating the 8-wk well-child visit to age 6 wk.[1,8] While the administration of subsequent doses of some vaccines could be similarly adjusted, the opportunity cost of shifting the current vaccination schedule must be recognized against the benefit of doing so. Finally, although it is likely—given the current recommended childhood vaccination schedule—that most children receive their 1st dose of RV vaccine at or near age 8 wk in clinical practice, it is undoubtedly the case that some children are vaccinated earlier (as early as 6 wk of age) while others are vaccinated later (as late as ~14 wk of age). To the extent that a disproportionate percentage of children are vaccinated earlier or later than age 8 wk, the results of this study may not be fully generalizable to clinical practice.

In conclusion, the results of our study suggest that accelerating the dose-regimen for RV vaccination may reduce the number of RV-related encounters by 9–14% among children aged <6 mo in US clinical practice.

Patients and Methods

Model overview

We developed a cohort model to depict annual rates of medically-attended RVGE among US children less than 6 mo of age, as well as the expected impact of RV vaccination. Alternative strategies for vaccination with RV1 and RV5 were considered, including: administration of vaccine doses consistent with ACIP recommendations ("Base Case" schedule),[1] accelerating the 1st dose of vaccine only, and accelerating the 1st and subsequent doses of vaccine. Schedules for the Base Case and accelerated vaccination regimens are described below under Vaccine Schedules.

Expected outcomes were tallied on a weekly basis over a 1-yr period by combining age-specific data on rates of medically-attended RVGE and corresponding estimates of population size. Medically-attended RVGE was stratified by healthcare setting, and included episodes resulting in hospitalization, an ED visit, and an outpatient visit (i.e., physician office or hospital ambulatory). Reductions in RVGE rates from vaccination were calculated by further combining age-specific data on vaccine coverage and vaccine effectiveness, the latter conditional on the assumed number of doses received. Model outcomes included the expected

total annual numbers of RVGE cases requiring hospitalization, an ED visit, and an outpatient visit, respectively. The costs of vaccination with RV1 and RV5 were not considered.

Model estimation
Population demographics

The estimated size of the US population aged less than 6 mo (2.1 million children) was obtained from US Census Bureau data for calendar year 2011.[14] In each week of the 1-yr modeling period, the population was equally divided into 26 ([365.25 d/7 d]/2) mutually-exclusive and mutually-exhaustive subgroups based on age in weeks (n = 81060). Although the size of the model population was assumed to be constant during the 1-yr observation period, the model population was dynamic allowing children to be born into, and age out of it.

Rates of RVGE
Pre-vaccination era

Age-specific rates of RVGE requiring hospitalization were based on surveillance data collected from 1997–2002 and 2005–2006 at Cincinnati Children's Hospital Medical Center, which provided care for more than 97% of Hamilton County children requiring hospitalization (**Table 3**).[9] In this study by Staat et al., cases of RVGE were identified using data from 2 independent surveillance systems: an active surveillance system for enteric infections and a passive surveillance system comprising test results generated in the provision of medical care.

Age-specific rates of RVGE requiring an ED or an outpatient visit were estimated by allocating corresponding rates for children aged less than 3 y from Payne et al. across monthly age bands (0 to <3, 3 to <6, 6 to <12, 12 to <24, 24 to <36 mo)[10] based on the calculated distribution of (hospitalized) cases from Staat et al.[9] In the study by Payne and colleagues, the cumulative incidence of RVGE requiring ED visits was estimated using published data from the Centers for Disease Control and Prevention's New Vaccine Surveillance Network, which conducted prospective, population-based surveillance from January 2006–June 2006 for acute gastroenteritis at 3 sites in 3 US counties-Vanderbilt University Medical Center (Davidson County, Tennessee), Cincinnati Children's Hospital Medical Center (CCHMC) (Hamilton County, Ohio), and the University of Rochester Medical Center (Monroe County, New York).

The cumulative incidence of RVGE requiring outpatient care was estimated by Payne et al. using an "indirect method," by combining data from National Health Care Surveys on the number of outpatient encounters and conditional probabilities that such encounters were due to RV. RVGE rates for children aged 0 to <3 mo and 3 to <6 mo were assumed to be constant within these bands when further stratified by age on a weekly basis.[10]

Post-vaccination era

The 'herd effect' or 'indirect effect' from widespread use of RV vaccination was accounted for by reducing disease rates from the pre-vaccination period. Expected indirect effects were based on the data from a retrospective evaluation of healthcare utilization for RV-coded diarrhea in US children and estimated reductions in disease among unvaccinated children.[5] Indirect effects

were estimated in this study by comparing rates of RV disease in the post-vaccine era (2008 and 2009, respectively) to that in the pre-vaccine era (2002–2006). Because estimated indirect effects were markedly different in 2008 than 2009, we conservatively employed the higher values of indirect effects to estimate rates of RVGE in the post-vaccination era (as a result, less disease was assumed to be preventable with [accelerated] vaccination).

Vaccine effectiveness

Effectiveness of RV1 and RV5 was based on estimates set forth by Jit et al. in their updated evaluation of the cost-effectiveness of RV vaccination in 5 European countries.[11] In their study, Jit and colleagues used data from the pivotal Phase III trial of RV5, as well as several post-hoc sub-studies of the pivotal trial to estimate vaccine effectiveness from receipt of dose 1 to dose 2, dose 2 to dose 3, and dose 3 through the end of the RV season.[2,15] For RV1, Jit et al. based their estimates of 1-dose and 2-dose effectiveness on data from one of the pivotal trials that was conducted in Europe.[4] Because not all of the estimates of vaccine effectiveness required for the Jit cost-effectiveness model were explicitly evaluated and reported in the pivotal trials, Jit and colleagues employed available data from these trials to derive the missing values. Since our model considered disease burden during a relatively brief period of time (i.e., from birth to 6 mo of age), vaccine effectiveness was assumed not to wane during this period.

Vaccination schedules

For RV1, 3 alternative vaccination schedules were considered:
1) Base Case: dose 1 at 8 wk, dose 2 at 16 wk
2) Accelerated 1st dose: dose 1 at 6 wk, dose 2 at 16 wk
3) Accelerated 1st/2nd dose: dose 1 at 6 wk, dose 2 at 10 wk

Accelerated schedules were based on the minimum age at receipt of 1st dose and the minimum interval between the 1st and 2nd doses.[6,7]

For RV5, 4 alternative vaccination schedules were considered:
1) Base Case: dose 1 at 8 wk, dose 2 at 16 wk, dose 3 at 24 wk
2) Accelerated 1st dose: dose 1 at 6 wk, dose 2 at 16 wk, dose 3 at 24 wk
3) Accelerated 1st/2nd dose: dose 1 at 6 wk, dose 2 at 10 wk, dose 3 at 24 wk
4) Accelerated 1st/2nd/3rd dose: dose 1 at 6 wk, dose 2 at 10 wk, dose 3 at 14 wk

Accelerated vaccination was assumed to confer earlier protection against RVGE-related encounters—relative to the Base Case Schedule—without an adverse impact on vaccine efficacy, vaccine safety, or vaccine coverage. In the aforementioned pivotal clinical trials for vaccine efficacy, safety, and immunogenicity, children were enrolled as early as 6 wk of age.[2-4]

Analyses

Outcomes for each of the alternative vaccination schedules were estimated assuming that children received vaccine at levels consistent with those reported in a recent publication by Eisenberg et al. on adherence with RV immunization in US clinical practice (**Table 4**).[16] Based on the Eisenberg study, 27% of children were unvaccinated, 6% were vaccinated with RV1 and 67% were vaccinated with RV5. Among children receiving RV1, 15% received only 1 dose and 85% received 2 doses; among those receiving RV5, 7% received only 1 dose, 17% received only 2 doses, and 76% received all 3 doses.

Children not receiving any doses of vaccine were thus assumed to be unprotected until 6 mo of age, while those only partially vaccinated were assumed to receive partial protection (as described under Vaccine Effectiveness). Among fully-vaccinated children, all were assumed to be unprotected against RV infection before receipt of dose 1, partially protected during the course of vaccination schedule, and fully protected following receipt of the last dose (as described under Vaccine Effectiveness).

For purposes of comparison, model outcomes also were estimated assuming all children in the model population would receive RV vaccine (RV5, 92%; RV1, 8%) and that all children would be fully immunized, per the alternative vaccination schedules. In these analyses, children assumed to be unvaccinated in the previous scenario (i.e., the 27%) were distributed proportionally to receive RV5 and RV1, respectively. Model outcomes also were estimated assuming that only RV5 and, alternatively, only RV1 was available for use.

One-way deterministic sensitivity analyses were conducted to assess the robustness of findings with respect to changes in key parameter estimates, including the risks of RVGE-related encounters, indirect effects of RV vaccination, and vaccine effectiveness. Upper and lower bounds for RVGE-related risks and indirect effects were based on corresponding 95% confidence intervals from the source materials.[5,9,10] Upper and lower bounds for effectiveness of RV1 (2 doses) against hospitalization was based on data from the aforementioned pivotal clinical trial[4]; because measures of uncertainty were not available for other estimates of vaccine effectiveness, upper and lower bounds for the estimates were derived assuming proportionality with the values for 2-dose RV1 effectiveness.

Acknowledgments

Trademark Statement

Rotarix is a registered trademark of the GlaxoSmithKline Group of Companies. Rotateq is a registered trademark of Merck and Co., Inc.

Supplemental Materials

Supplemental materials may be found here: www.landesbioscience.com/journals/vaccines/article/28689

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