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BRIEF REPORT

Vaccine discontinuation and switching following regulatory interventions in response to rotavirus vaccine contamination with porcine circovirus DNA fragments

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ABSTRACT

Purpose The Food and Drug Administration temporarily suspended monovalent rotavirus vaccine (RV1) use following discovery of contamination with porcine circovirus fragments and subsequently announced similar contamination of the pentavalent rotavirus vaccine (RV5) but recommended continued use of the product. We assessed the utilization of these vaccines in relation to the announcements.

Methods Using claims submitted to a commercial health insurer for administration of RV1 and RV5, we estimated the number of administrations of the vaccines and the extent of switching between RV1 and RV5. Procedure codes on submitted claims identified vaccine administrations among infants ≤ 1 year old through 16 June 2010. Among infants who received a first dose of vaccine before the corresponding announcement, and whose second dose was anticipated following the announcement, we estimated the number who received no second dose of rotavirus vaccine.

Results There were 31 178 RV1 initiators and 514 357 RV5 initiators. We observed a 93% reduction in RV1 doses in the month following the recommended suspension of use, coupled with extensive switching to RV5 (90% of subsequent doses) and a reduction in second RV1 doses (from 35.5% incomplete to 40.9%). There was a 15% increase in number of RV5 administrations following announcement of its contamination, with little switching to RV1 but with a possible decrease in completion.

Conclusions Recommended suspension of RV1 use led to a substantial decrease in use and extensive switching to RV5. The announcement that RV5 was similarly contaminated, but without a corresponding recommendation to suspend use, had little effect on use.

KEY WORDS—pharmacoepidemiology; health insurance claims data; rotavirus vaccine; vaccine safety; risk management

Abbreviations: RV1: monovalent live-attenuated human rotavirus vaccine; RV5: live, oral, pentavalent rotavirus vaccine; PCV: porcine circovirus; ICD-9: International Classification of Disease, 9th revision; CPT: Common Procedural Terminology; FDA: Food and Drug Administration

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INTRODUCTION

The monovalent live-attenuated human rotavirus vaccine (RV1) was licensed by the US Food and Drug Administration (FDA) in April 2008, approximately two years following the agency's approval of the live, oral, pentavalent rotavirus vaccine (RV5).[1] By early 2010, RV1 accounted for 25% of the rotavirus vaccine market in the USA.[1] On 22 March 2010, the FDA released an Early Communication that recommended the temporary suspension of RV1 use following discovery of contamination by DNA particles from potentially infectious porcine circovirus (PCV) 1.[2]

Although there are no known health effects of PCV 1 in humans,[3] the suspension was instituted pending

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the outcome of a FDA Vaccines and Related Biological Products Advisory Committee meeting on 7 May 2010. In conjunction with that meeting, the FDA announced that RV5 also was contaminated with non-infectious and smaller DNA particles from PCV 1 and 2, therefore carrying a lower theoretical risk of infection.[4,5] At that time, following the advice of the advisory committee, the FDA recommended that both RV1 and RV5 were safe for continued administration based on their strong safety records and perhaps because the benefit–risk considerations were altered because no uncontaminated vaccine remained available.[6]

Because communicative interventions by regulators have had variable effectiveness and resulted in some unintended consequences,[7–10] we assessed the effect of the vaccine contamination announcements and recommended suspension of RV1, but not RV5, on the initiation and completion of the affected vaccines using data from a US health insurer.

METHODS

Following the announcement, we received daily claims submitted to a large, national commercial health insurer, which we added to a repository of claims data generated for reimbursement of healthcare services. These claims use International Classification of Disease, 9th revision (ICD-9), and Common Procedural Terminology (CPT) codes.

The study population consisted of infants less than one year of age who received RV1 or RV5. CPT codes identified administrations of the vaccines (90681 for RV1, 90680 for RV5) from the date of vaccine availability in the USA (August 2008 for RV1 and April 2006 for RV5) through 16 June 2010.

We estimated the number of daily administrations of RV1 and RV5 in the insured population and the extent of switching between RV1 and RV5 before and after the 22 March 2010 suspension announcement for RV1 and the 6 May 2010 contamination announcement for RV5. Claims indicating a second dose of rotavirus vaccine were counted if they occurred at least 21 days following the previous claim.

Among infants who received a first dose of RV1 before the announcement, and whose second dose was anticipated following the announcement,[11] we estimated the number who received no second dose of rotavirus vaccine. This analysis included infants who received their first dose of RV1 30−60 days prior to the RV1 suspension. Similarly, we assessed utilization of RV5 in the period around the initial announcement (without suspension) that the product was contaminated. We estimated the number of daily administrations of RV5 before and after the 6 May 2010 announcement and estimated among children who had a first or second dose of RV5 in the 30–60 days before the May announcement, the number that appeared to receive a subsequent dose.

RESULTS

There were 31 178 infants who initiated RV1, 14 831 (48.5%) of whom were girls (Table 1), and 514 357 RV5-exposed infants, 48.9% of whom were girls. After the RV1 announcement, we observed few first or second doses of RV1 (Figure 1). There were 281 doses of RV1 administered in the 30 days following the announcement compared with 3804 doses in the 30 days leading up to the announcement, a 93% absolute reduction. In contrast to RV1, we observed no appreciable decrease in use following the announcement that RV5 was contaminated with PCV 1 and 2. There were 17 473 doses of RV5 administration in the 30 days prior to the announcement of PCV contamination, compared with 20 361 doses administered in the subsequent 30 days, a 15% increase.

Among the 21 388 RV1 initiators who received a second dose of rotavirus vaccine through the health plan on or before the date of the announcement, 9.6% switched to RV5 for the remaining doses. This proportion increased to 90.4% following the announcement. With RV5, 376 040 infants received a second dose, and 98% received this second dose with RV5, a proportion that did not change with the contamination announcement.

Among the 2408 infants who initiated RV1 in the 30−60 days prior to the FDA suspension, 979 (40.9%) received no second dose of rotavirus vaccine

Table 1. Demographic characteristics of infants who received the monovalent or pentavalent human rotavirus vaccines in the commercial health insurance claims data, 16 April 2006 to 16 June 2010

	RV1		RV5	
	n = 31 178		*n* = 514 357	
	n	%	*n*	%
Age, months				
0–2	5678	17.1	82 293	16.0
3–4	23 212	70.0	313 327	60.9
5–6	3590	10.8	71 289	13.9
>6	698	2.1	47 448	9.2
Girls	16 077	48.5	251 635	48.9
Boys	17 101	51.5	262 722	51.1
Geographic region				
Midwest	8346	25.2	125 494	24.4
Northeast	6111	18.4	73 732	14.3
South	13 880	41.8	225 572	43.9
West	4841	14.6	89 559	17.4

RV1, monovalent live-attenuated human rotavirus vaccine; RV5, live, oral, pentavalent rotavirus vaccine.

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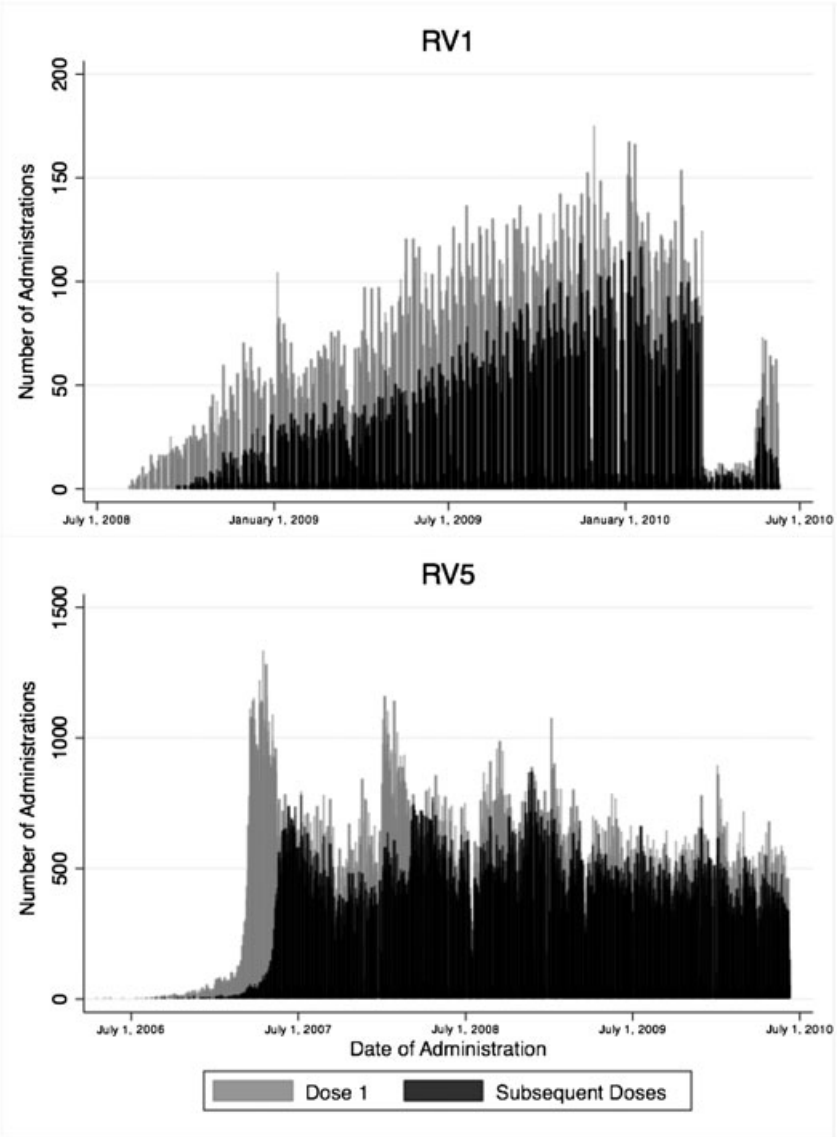

Figure 1. Daily number of infants exposed to the monovalent live-attenuated human rotavirus vaccine (RV1) and live, oral, pentavalent rotavirus vaccine (RV5) in a large national commercial health plan

through the health plan in the 60 days following the announcement, in comparison to 35.5% of infants who did not receive a second RV1 dose overall. In the RV5 cohort, 10 128 infants received a first dose in the 30−60 days prior to the RV5 contamination announcement, and 3691 (36.4%) received no subsequent dose, a somewhat higher fraction than the 26.9% of infants who did not receive a second dose through the health plan overall.

DISCUSSION

We observed a substantial and almost immediate reduction in first and second administrations of RV1 following the recommendation to suspend the product's use, demonstrating the effectiveness that such announcements can have on the use of the product. In the face of uncertainty about the optimal approach with RV1, some clinicians appear to have discontinued the rotavirus vaccine regimen altogether, whereas a substantial portion continued the regimen but switched to RV5 for the second dose. This option to switch between rotavirus vaccines had been a prior recommendation by the Advisory Committee on Immunization Practices.[11] The mid-course change from RV1 to RV5 is a straightforward modification of therapy: 3 doses instead of the 2 doses indicated with RV1.[11]

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With medications, potentially serious adverse effects can frequently be managed through therapeutic risk management programs in a way that maintains a favorable benefit–risk ratio.[12] The severity of the condition being treated enters this evaluation, and the decision to limit the use of medications frequently comes at the cost of not having adequate treatment for the target indication. Conversely, the target population for vaccines is usually healthy individuals so that a higher threshold for safety than with medications is usually appropriate.[13] This concern was demonstrated by the rapid removal of the first-generation rotavirus vaccine (rhesus-human rotavirus reassortant-tetravalent vaccine, RotaShield®), when its association with intussusception—a rare but potentially serious self-prolapse of the bowel—became known.[14] The intervention applied in this case (recommended suspension) likely reflects the uncertainty of potential health consequences from exposure to the viral DNA particles, instead of compelling evidence for an adverse health outcome (intussusception). However, the balance between public scrutiny of adverse vaccine effects and the public's acceptance of vaccination is difficult to achieve.[13] Had the FDA chosen not to recommend suspension of RV1 use, they would have placed the public at an unknown, potentially higher risk of adverse effects attributable to PCV DNA exposure. However, public health interventions can result in unintended consequences such as public distrust.[15]

The features of this case may have contributed to the sizeable response even in the absence of clear evidence of risk. As a vaccine, RV1 is intended to prevent disease rather than treat disease, so the risk–benefit threshold is lower than it is for many medications, especially in the USA where the absolute risk of harm from rotavirus infection is low. Furthermore, the vaccine is given to infants who might be considered a vulnerable population with a lower risk–benefit threshold. Finally, the availability of an alternative vaccine (RV5) made for a straightforward change in the RV1 regimen.

Once regulators make the decision to intervene at the population level, the choice of approach can be as complex as whether to intercede in the first place. Indeed, black box warnings and the announcements that accompany them have typically been associated with less effectiveness[7–9] than observed with RV1 in the present study. In a study of the impact of "Dear Healthcare Professional" Letters on prescribing of contraindicated drugs to patients using cisapride, the results showed no benefit of a single letter but a steady decline in co-dispensing of cisapride and contraindicated medicines associated with more intense publicity and direct intervention with dispensing pharmacies.[7] Moreover, with interventions that do not remove the medical product from use, regulators face the challenge that prescribers might disagree with the regulatory recommendation and continue the same or similar practices. In the case of the oral contraceptive ethinyl estradiol/drospirenone, which has a progestin (drospirenone) that possesses anti-mineralocorticoid activity, prescribers were generally aware of this unique characteristic of the progestin but disagreed about the role of serum potassium monitoring.[16]

In this study, we observed some evidence of potential, although probably modest, consequences of the FDA's interventions. We observed slightly lower vaccine regimen completion, although we cannot rule out the possibility that this finding was a result of lag time between administration of vaccines and submission of claims. We did observe that a slightly lower fraction of infants completed rotavirus vaccine courses in the present study than in previous studies of using the same data (73% vs 85%).[17] However, in these data, claims for 90% of vaccine administrations are captured within 30 days, mitigating incomplete capture. Although this finding was of a small magnitude, it could plausibly result in an increased risk of rotavirus gastroenteritis, given the effectiveness of the vaccines, although population benefit may be maintained through herd immunity.[18]

This evaluation of the effect of the FDA announcement is based on health insurance claims submitted by providers, which were assumed to reflect the product used. In these data, codes for RV1 and RV5 are correct at least 90% of the time so that misclassification of the vaccine is an implausible explanation for our findings.[19] Additionally, our analysis assumes that infants were continuously enrolled in the health plan during observation so that claims would be observed if they received a vaccination (this assumption is more likely met among infants for whom claims were received). Violation of this assumption would tend to underestimate the number of doses administered with less effect among those who received the vaccine. Because enrollment in the underlying health insurance plans is primarily determined through employment, and because people change jobs (and therefore insurance plans), there is frequent turnover in commercial health insurance databases. The average duration of enrollment in the data we used is approximately two years. This turnover results in censoring of observations such that second and subsequent doses are incompletely observed. Our analysis assumes that censoring is unrelated to vaccinations so that while we underestimated absolute completion, the comparisons of completion are likely to be valid. Finally,

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the effectiveness of this FDA announcement may not generalize to other FDA announcements, even with vaccines.

In summary, we observed that the FDA's recommendation to suspend use of RV1 following discovery of contamination with PCV DNA fragments resulted in a substantial decrease in use of the product. Contrastingly, the FDA's announcement (without a corresponding suspension) that RV5 was similarly contaminated had no appreciable effect on overall use of the vaccine. Both interventions appeared to result in a small decrease in vaccine course completion.

CONFLICT OF INTEREST

This study was funded internally by OptumInsight, a division of UnitedHealth Group. At the time of this study, the authors were employees of OptumInsight. Drs Dore and Seeger have worked on a research project funded by GSK Biologicals, manufacturer of the monovalent live-attenuated human rotavirus vaccine. Dr Seeger has additionally worked on a research project funded by Merck, manufacturer of the live, oral, pentavalent rotavirus vaccine. These studies were unrelated to this work.

KEY POINTS

- Utilization of the monovalent rotavirus vaccine was reduced by 93% following the Food and Drug Administration's recommendation to stop the use of the product following discovery of contamination with DNA fragments from porcine circovirus.
- About 90% of infants who discontinued the monovalent rotavirus vaccine completed the regimen with the pentavalent rotavirus vaccine.
- A similar announcement that the pentavalent rotavirus vaccine was contaminated, but without the corresponding recommendation to suspend the use of the product, resulted in no switching.

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