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Co-administration with Men-B vaccine increases Rotavirus vaccination coverage: A 5-year regionwide retrospective cohort study (STORM study)

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ABSTRACT

Introduction: In Italy Rotavirus vaccination (RVV) is provided free of charge from 2018, however, the coverage is scattered and suboptimal. The narrow time frame to complete the schedule is a barrier to uptake, and co-administration with other vaccines may potentially increase the coverage. Although the co-administration of RV vaccine and Meningococcal Group B vaccine (MenB) is not included in the product labels, we aimed at studying its impact on RVV coverage.

Methods: This Surveillance study on Timing and cOverage of Rotavirus and MenB vaccine co-administration (STORM study) used the Regional Vaccination Registry to collect data about children born in Campania Region between January 2016 and December 2020, and receiving vaccines scheduled in the first year of life.

Results: Among the 224,110 children enrolled, 60,614 (27.0%) completed the RVV schedule, with a vaccination rate that increased over time from 1.15% in 2016 to 56.92% in 2020.

The first and last dose of RVV schedule were administered beyond the recommended time in 6% of the study population, respectively.

Co-administration of RV vaccine with MenB vaccine increased from 0.7 % in 2016 to 46.85 % in 2020. Children receiving RV/MenB vaccines concomitantly had a significantly higher chance of completing the RV schedule compared to those receiving RVV alone during a specific appointment (94.78 % vs 72.26 %, Prevalence Ratio -PR- 1.275, 95 %CI 1.245–1.295p < 0.00001). The positive driving effect of RV/MenB co-administration was more evident for children receiving pentavalent (PR 1.288) than monovalent RVV (PR 1.115) which was confirmed when adjusted for confounding variables (i.e., year of vaccination, local district, gender).

Conclusions: Although still far from the target, RVV coverage has increased in recent years in Campania Region. Co-administration with MenB vaccine may aid in increasing RVV coverage, especially for pentavalent RVV. Further safety data are needed to support co-administration as a key tool to increase coverage.

1. Introduction

Rotavirus (RV) is the leading cause of acute gastroenteritis (AGE) worldwide and a major reason for medical visits and hospitalization in children [1,2]. The implementation of immunization programs against RV led to a reduction in AGE episodes, medical visits, and hospital admissions in countries that reached a high vaccination coverage [2].

Two oral live-attenuated vaccines against RV are licensed in Europe for children in the first year of life: a human monovalent vaccine (RV1) and a human bovine pentavalent reassortant vaccine (RV5). Both have good safety and efficacy profiles and can be administered from the sixth week of life.

RV1 vaccine, containing G1P [8] strain, is administered as a two-dose schedule, with a minimum interval of 4 weeks between doses, in order to complete the vaccination course within 24 weeks. RV5 vaccine, containing G1, G2, G3, G4 and P1 A(8) strains, is administered as a three dose schedule and should be completed within 32 weeks (Table S1). The timing of administration of the second dose of RV5 is not scheduled,

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however, an interval of at least 4 weeks between doses is recommended.

In Italy, vaccination against RV has been included in the 2017–2019 National Immunization Plan (NIP) and is strongly recommended and provided as an active and free offering starting from the pediatric cohort born in 2018. Nevertheless, vaccination still has a scattered and sub-optimal coverage throughout the national territory (National Vaccination Prevention Plan 2017–2019) [3]. The main reason may be related to a delay in starting the vaccination courses, which may lead to an incomplete RV vaccination schedule, and to the dense immunization schedule of the first year of life, which particularly hampers the three-dose RV immunization schedule.

The co-administration of RV vaccines with other vaccines may be a chance to optimize the vaccination schedule. The co-administration with hexavalent and pneumococcal conjugate vaccines has been tested and approved by European Medicines Agency [4,5]. In contrast, the co-administration with meningococcal group B (MenB) vaccine, while supported by limited scientific evidence, is not currently included in the summary of the product characteristics (SmPC) and could exert a driving force to increase the uptake of RV immunization.

O'Ryan et al. reported anecdotal MenB and RV vaccines co-administration during two pivotal clinical trials of MenB vaccine with comparable reactogenicity and safety profiles in those who did and did not receive RV vaccine [6]. In the UK, the national vaccination program approved the co-administration of MenB and RV vaccines since 2018 [7]. More recently, a systematic review analyzing the safety profile of RV vaccination in more than 600,000 children did not identify new safety concerns upon co-administration with meningococcal vaccines in terms of fever, diarrhea, vomiting, change in eating habits, and intussusception [8]. MenB and RV vaccines are also routinely co-administered as part of the Primary Childhood Immunisation Schedule in Ireland [9].

In our region at the end of 2019, the Regional Health Bureau released a document reviewing the timing of RV vaccine administration allowing the administration of mixed RV vaccine schedule (RV1 and RV5) and the co-administration with any other vaccine (including MenB vaccine), although the routine clearance by health and safety authorities were pending or not available.

The co-administration of RV and MenB vaccines could increase vaccine uptake, reduce vaccine appointments allowing for a timely completion of the RV immunization schedule.

The aims of this study were to investigate the immunization coverage and the timing of administration for RV vaccines in a large sample size and, specifically, to assess the impact of co-administration with MenB vaccine on the RV vaccine coverage.

2. Methods

The present retrospective Surveillance study on Timing and cOverage of Rotavirus and Men-B vaccine co-administration (STORM study) was conducted on the entire cohort of children born in Campania Region between January 1st 2016 and December 31st 2020, receiving vaccines scheduled in the first year of life (RV, MenB, hexavalent, pneumococcal conjugate).

2.1. Setting and study design

Campania Region has an overall population of approximately 5.5 million inhabitants with an estimated 800,000 residents aged <14 years and 45,000 newborns yearly. In Campania, as in all Italian regions, the Vaccination Centers are responsible for the organization and administration of vaccination as well as for overseeing implementation of vaccinations and monitoring coverage. The territorial distribution of Vaccination Centers depends on the number of inhabitants, density of population, number of new births and distance from other districts.

All children born in Campania Region eligible for vaccination were enrolled in this study, including migrants and foreigners without a residence permit, without distinction of race, ethnicity and gender, recorded or not to local primary Care Pediatricians.

Data was extrapolated from the Vaccination Registry of Campania Region ("Gestione Vaccini"-GEVA Registry).

This regional electronic immunization register is currently used for the entire immunization process from vaccination call-out, to assess the vaccination coverage, up to sending aggregated data to the Ministry of Health to estimate the national vaccination coverage.

Anonymized data obtained by the GEVA Registry was used to analyze vaccination coverage according to age and cohort, timing of administration, frequency and type of co-administration. The characteristics of each vaccine administered were recorded (i.e., brand, number of doses) as well as the lapse of time between vaccination and possible delay.

2.2. Definition of appropriateness of Rotavirus vaccine uptake

RV vaccination schedule was considered as complete if any single child received 2 doses of RV1 or 3 doses of RV5 at least 4 weeks apart. Children receiving only one dose of RV1 or, alternatively, 1 or 2 doses of RV5 were considered as partially vaccinated against RV.

Mixed RV schedule was considered "complete" if it included three doses of any RV vaccine (RV1 + RV5 + RV5, RV5 + RV5 + RV1, RV5 + RV1 + RV1), otherwise the schedule with only two different doses was considered "incomplete".

Time of administration was expressed in weeks of age to better define appropriateness of vaccine uptake.

As of timing of administration, according to product labels, we considered completing the RV vaccination schedule within 24 weeks of age for RV1 and 32 weeks of age for RV5, as "recommended" timing. In contrast, receiving the last dose of RV1 vaccine between 24 and 32 weeks of age was considered as a "delayed" timing, in accordance with recommendations provided by American Academy of Pediatrics and by local regional indications (DL. 0746512).

We investigated possible differences in terms of immunization coverage and appropriateness in timing of administration comparing children receiving RV vaccine doses alone and concomitantly with other vaccines, mainly with MenB vaccine doses.

2.3. Ethical aspects

The study protocol followed the criteria postulated by the declaration of Helsinki and was approved by the Ethical and Scientific Committee of the University of Naples "Federico II" (STORM Study, N.432/21 approved on 27/12/2021) and is registered on ClinicalTrials.gov (NCT05212935).

Caregivers' consent to the use of anonymized data about vaccine uptake is routinely acquired by healthcare authorities at the beginning of vaccine schedule for each child and recorded into the GEVA Registry. All data are anonymized by using single patient consecutive codes, and neither the study coordinator nor other investigators taking part in the present study were able to reconduct sensitive data to single patients. Hence, a specific patients' consent was not required for the study protocol.

2.4. Statistical analysis

Descriptive statistics were applied as appropriate. Multivariable Poisson regression models were used to compute vaccination coverage ratios, setting eligible population for the vaccination as offset. Models were first adjusted for administration year (as categorical variable; partially adjusted models) and subsequently for local health authority (ASL Avellino, Benevento, Caserta, Napoli 1 Centro, Napoli 2 Nord, Napoli 3 Sud, and Salerno). Results were presented as prevalence ratios (PR) and 95 % confidence intervals (95 % CI). Stata MP 17.0 was the statistical software used for data analysis.

In a preliminary analysis of data, we identified a subgroup of patients (n = 1566, 0.7 % of the entire population) in which the RV vaccine product was not specifically reported in the database. In that case, children receiving 1 dose were considered as partially vaccinated, and those with registration of three doses classified as completely vaccinated. However, children who received 2 doses of a non-specified RV vaccine, were indicated as not assessable (since it is impossible to establish whether they received a complete schedule of RV1 or incomplete of RV5) and excluded from the main statistical analysis. However, we conducted a further sensitivity analysis to address this aspect labeling all children who have received 2 doses of a non-specified RV vaccine as receiving an incomplete schedule.

3. Results

3.1. Coverage and timing of administration

A total of 224,110 children born in the Region during the study period were enrolled in the study. During the 5 years of observation only 346 (0.15 %) children did not receive any vaccination recommended by the National vaccination schedule in the first year of life (pneumococcal, hexavalent, rotavirus).

Overall, 75,885 children (33.65 %) received a first dose of any RV vaccine in the study period: 68,146 (89.8 %) received RV5, 5696 (7.51 %) received RV1. In a minority of children (2043, 2.69 %), RV vaccine product was not specified in the dataset. RV5 was more widely distributed in the Region, and its uptake increased overtime (Fig. 1).

RV vaccination schedule was completed in 60,614 (27.0 %) according to the SmPC, 15,271 (6.13 %) children received an incomplete schedule and 148,225 (66.2 %) were not vaccinated against RV (Fig. 2, Table S2). In the subgroup of children whose details of the RV vaccine product were not reported in the dataset, 477 (0.21 %) received only one dose of (unspecified) RV vaccine and other 1566 (0.7 %) received 2 doses. In the main analysis, these children were included among those with incomplete schedule.

Of note, 1693 children who represent the 2.2 % of those receiving at least one dose of RV vaccine, received a mixed schedule with at least one dose of either RV1 and RV5 vaccines. Of them 749 (44.2 %) received a "*completed mixed schedule*". A further 944 (55.8 %) received 2 doses of RV vaccine (RV5 + RV1 or RV1 + RV5), so their schedule was considered incomplete.

The rate of fully vaccinated children increased during the study period (from 1.15 % to 56.92 %), especially in 2018 after the active and free offering, with a 15-fold increase over the previous years. The rate of children who received the first dose of RV vaccine but did not complete the schedule increased overtime from 0.14 % to 11.0 % (Table S3).

Among children receiving a first dose RV vaccine, the proportion of those who completed the immunization schedule was quite stable overtime and ranged between 83 and 89 %. Comparing the two different schedules, children receiving RV1 had a significantly higher chance to complete RV vaccination compared to those receiving RV5 (91.1 % versus 81.3 % p < 0.00001) (Fig. S1). However, despite the number of doses needed to complete each schedule, it should be taken into account that only a small proportion (<10 %) of the entire regional population received RV1.

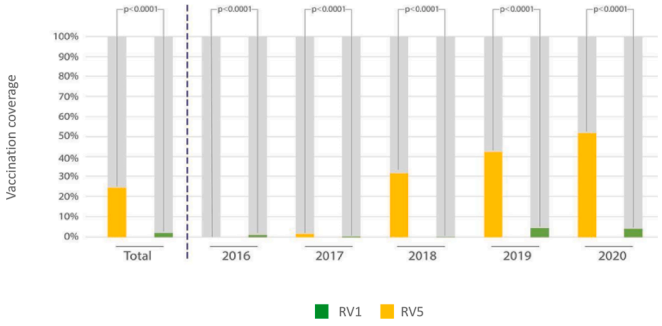

Fig. 1. Total and annual immunization coverage according to the RV vaccine product. The figure depicts the overall Rotavirus (RV) immunization coverage and the annual vaccine uptake of the two RV-vaccines available on the regional market from 2016 to 2020. Chi square test was used to compare the annual uptake of the two RV vaccines, p value <0.05 was considered statistically significant.

The first RV vaccine dose was administered within 12 weeks of age in 57,792 (76.16 %) children (Table 1), with a further 13,660 (18 %) children receiving the first dose between 12 and 15 weeks. About 6 % of children received their first dose of RV vaccination after 15 weeks of life (Table 1). Among fully vaccinated children, RV5 was completed within the recommended timing according to SmPc in 93.7 % of children compared to RV1 in 86.8 % (p < 0.00001), and 11.9 % of children completed RV1 schedule between 24 and 32 weeks. (Table 1).

On average, the second dose was administered 53.4 ± 23.01 days after the first dose, without difference between RV1 (59.93 ± 23.5 days) and RV5 (52.71 ± 22.7 days).

3.2. Co-administration of RV/Men-B vaccines and impact on RV vaccination coverage

In most cases RV vaccine doses were administered together with one or more vaccines included in the NIP for the first year of life. The most commonly co-adminstered vaccine together with RV was the hexavalent vaccine (up to 80 % for the first dose) (Table 2).

About 35 % of children immunized against RV received their doses together with MenB vaccine. The co-administration RV/MenB vaccine increased overtime, from 0.7 % in 2016 to 46.85 % in 2020 (Fig. S2), with 27,175(91.7 %) subjects receiving RV5 and 823 (3.12 %) RV1.

In the main analysis, a higher proportion of children receiving RV/MenB vaccine co-administration completed RV schedule compared to those receiving RV vaccine alone during a specific appointment (94.78 % vs 74.36 % p < 0.00001). This evidence was also confirmed in the sensitivity analysis, when considering these children as partially vaccinated (94.19 % vs 72.26 % p < 0.00001) (Figs. 3 and 4, Tables S4 and S5).

4. Discussion

RV immunization rates are still suboptimal in several European Countries. Many different barriers hamper the implementation of this vaccination in different settings [2], including the timing of administration and the dense immunization schedule of the first year of life, the specific administration and reimbursement strategies in different countries, the low perception of the clinical risk from health-care professionals and families, and the fear of side effects.

In this regionwide 5-year retrospective study, we observed a progressive increase in RV vaccination rates and demonstrated that co-administration with MenB vaccines is associated with a significant increase in RV vaccine uptake and a higher chance of RVVschedule completion. Several studies and literature reviews have confirmed the effectiveness of RV vaccines. An observational study conducted in England and Wales showed a 77 % decrease in laboratory-confirmed Rotavirus infections and more than one fourth drop in all-cause AGE–associated hospitalizations compared with the pre-vaccination era [10]. In parallel, in high-mortality settings, the implementation of RV vaccination was associated with 30 % reduction in AGE mortality among children <1 year of age and 40 % in children <5 years of age [11]. Unfortunately, still today, the vaccine effectiveness observed in low-income settings, that suffer from a high Rotavirus and diarrheal mortality, is significantly lower than that seen in high-income populations [12,13].

The Italian National Vaccine Prevention Plan provided RV vaccination as an active and free offering starting from the pediatric cohort born

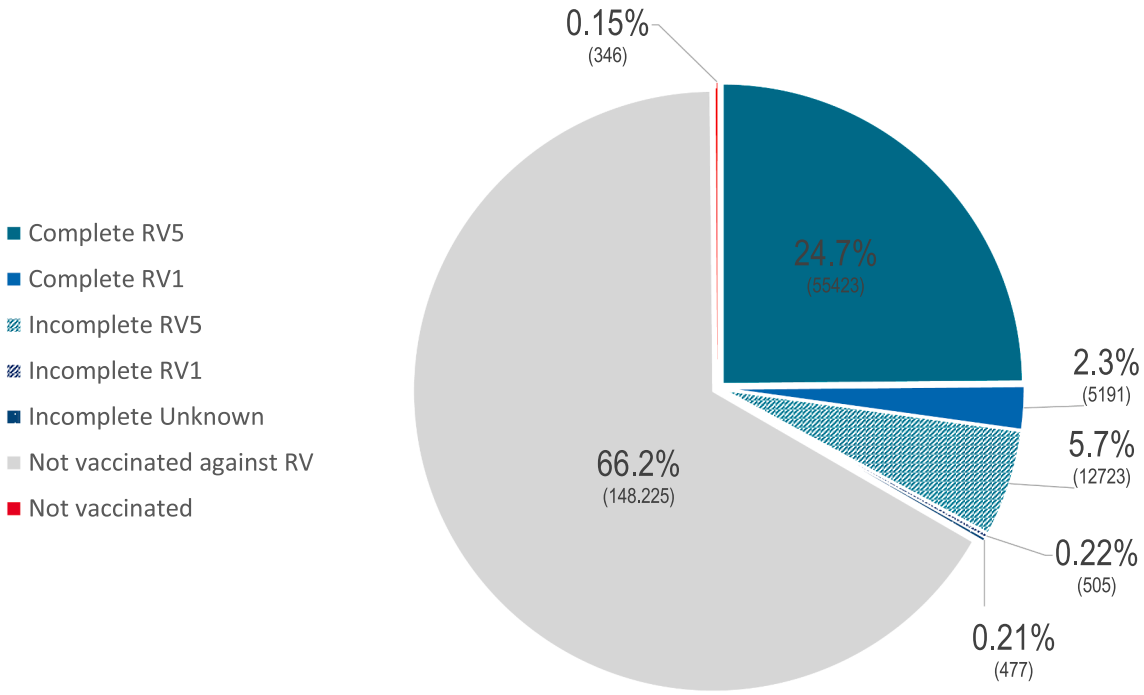

Fig. 2. Rotavirus Vaccine uptake in children living in Campania Region between 2016 and 2020. The figure shows the percentage of children who received a complete or incomplete RV immunization schedule, according to single RV vaccines, and those who were not vaccinated against RV or did not receive any vacciantion.

Table 1
Timing of RV vaccine doses administration according to RV product.

First dose	
Timing	N (%)
12 weeks	57,792 (76,16)
12–15 weeks	13,660 (18)
>15 weeks	4433 (5,84)
Total	75,885 (100)
Completed schedule	
Timing	**N (%)**
Recommended timing	56,462 (93,15)
Delayed* timing	620 (1,02)
Not recommended	3532 (5,83)
Total	60,614 (100)
RV5 complete schedule	
Timing	**N (%)**
<32 weeks	51,957 (93,75)
>32 weeks	3466 (6,25)
Total	55,423 (100)
RV1 complete schedule	
Timing	**N (%)**
<24 weeks	4505 (86,79)
24–32 weeks	620 (11,94)
>32 weeks	66 (1,27)
Total	5191 (100)

* Some Health Authorities (World Health Organization, America Academy of Pediatrics and the US Center for Disease Control and Prevention) allow a delayed administration of the first RV vaccine dose beyond the timing recommended by the manufacturer, Scientific Societies and most Authorities.

Table 2
RV vaccine co-administration with hexavalent and MenB vaccines according to RV vaccination doses.

	RV vaccination doses		
	1st	2nd	3rd
Children receiving RV vaccination dose	75,885	71,091	55,783
Number (%) of children receiving a co-administration with Hexavalent	60,757 (80.1)	30,988 (43.6)	23,507 (42.1)
Number (%) of children receiving a co-administration with Men-B	26,369 (34.8)	26,369 (37.1)	24,211 (43.4)

in 2018, and fixed the targets for immunization coverage, as follows: ≥60 % in 2018, ≥75 % in 2019 and ≥95 % in 2020 [14]. Campania Region is the largest and most populous region in the Southern Italy with more than 5 million residents including 1 million children. In this setting, the vaccination rate is still far from reaching the goal (approximately 50 % in 2019 and 2020), although, after the implementation of an active and free-of-charge offer from 2018, the coverage significantly increased. Similar data on vaccination coverage are reported in other European areas, despite differences observed between countries [15]. A recent systematic review reported data on RV coverage in the United States cohort, that reached a 74 % RV coverage in 2016, not meeting the 80 % target identified by the United States Healthy People agenda 2020 [16].

This suboptimal coverage particularly affects anti-RV prevention strategies, whose coverage rates in 2016 were significantly lower than that observed for other recommended childhood vaccines (≥90 %) either in United States or in Campania region [17]. Notably, we reported that only 0.15 % of children in Campania Region did not receive other vaccinations during the 5 years of observation, as a possible consequence of absolute vaccine contraindications, patients' migration or caregiver's refusal (although determinates were not investigated).

In our population about 6 % of children who received a first dose of RV vaccine did not complete the schedule. This finding is in line with evidence coming from other European countries. In Belgium, the first

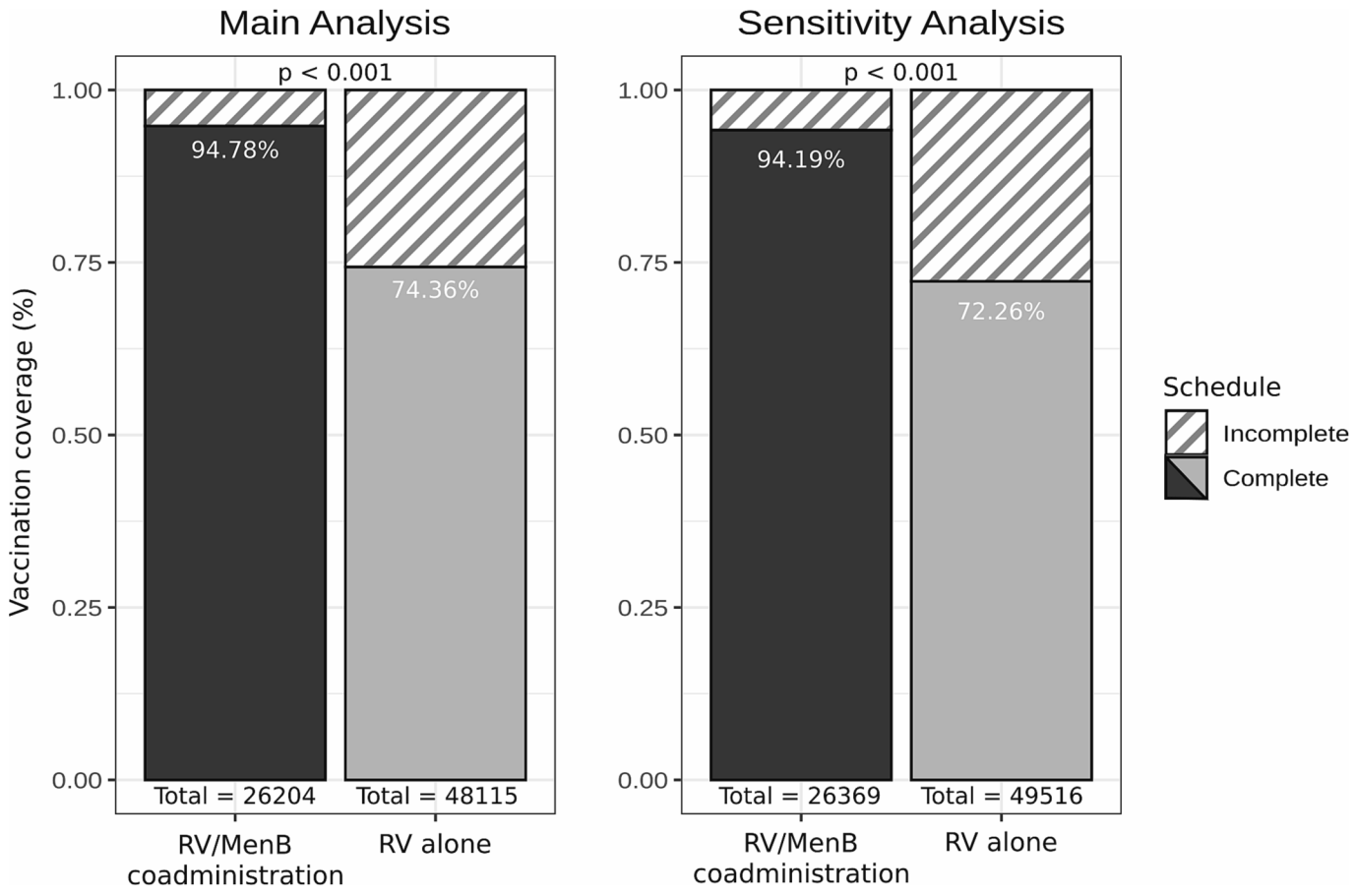

Fig. 3. Prevalence of complete RV vaccination schedule between children receiving RV vaccination alone or in coadministration with Men B. The figure depicts the percentage of children who completed RV schedule either if receiving a co-administration of RV/MenB vaccines or RV vaccine alone. Chi square test was used to compare two groups, p value <0.05 was considered statistically significant. In the main analysis children who have received 2 doses of a non-specified RV vaccine were excluded, while in sensitivity analysis these children were considered as partially vaccinated. Black and gray bars represent complete RV vaccination schedule, striped bars represent incomplete RV vaccination schedule.

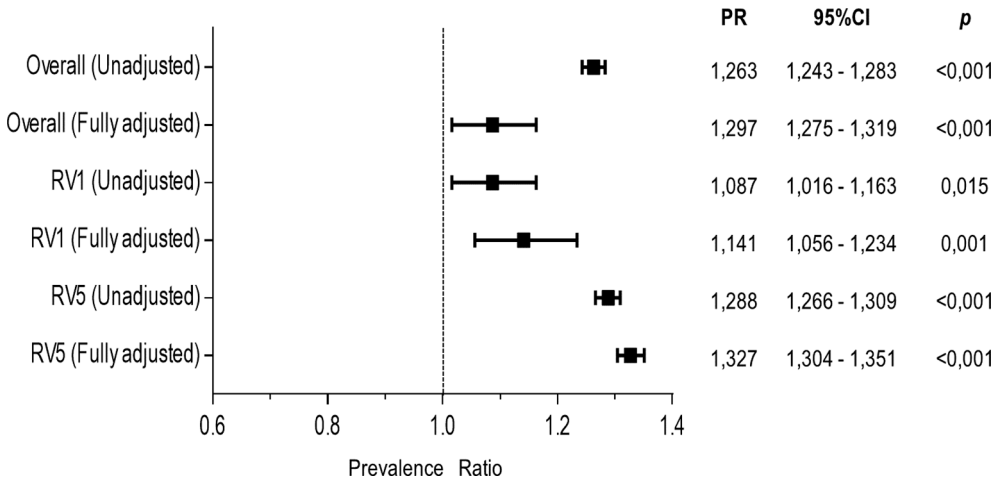

Fig. 4. Forest Plot on the impact of RV/MenB vaccine coadministration on the RV vaccination coverage. Sensitivity analysis reports prevalence ratio adjusted for confounding variables, including year of vaccination (partially adjusted), and local health district, vaccine cohort (fully adjusted). Results are presented as prevalence ratios (PR) and 95% confidence intervals (95%CI).

country to implement RV immunization in Europe and to reach the threshold of 80 % coverage, the proportion of children not completing the schedule reduce from 10.8 % in 2007 to 7.9 % in 2012 [18].

In this scenario, it is crucial to find strategies to optimize vaccination coverage. In our study population, we observed that RV vaccine doses were in most cases administered together with other vaccines included in the NIP schedule for the first year of life, and co-administration with hexavalent vaccines was observed for the first RV vaccine dose in up to 80 % of population.

RV vaccines are frequently administered together with other

vaccines, including hexavalent and pneumococcal vaccination, and no evidence of immunological interferences with other vaccines are currently reported [19,20]. However, data about the co-administration with Men-B vaccines are limited.

During the trialing of 4CMenB vaccines in European countries, where RV1 and RV5 where already licensed, over 300 children allocated to MenB vaccination concomitantly (and accidentally) received at least one dose of RV vaccines with no relevant effects on immunogenicity and safety [6]. Larger and reassuring data comes from United Kingdom and other countries where NIP encompasses the possibility of a coadministration of anti-RV and MenB vaccines, with no major consequences in terms of side effects. However, none of these studies was specifically aimed at investigating the incidence of side effects in children receiving the two vaccines concomitantly.

In our population of more than 200,000 children, we reported 35 % of co-administration of RV vaccines with MenB vaccines. The proportion of children concomitantly receiving the two vaccines increased overtime from 0.7 % in 2016 to 47 % in 2020.

Compared to children receiving RV vaccine with a separate appointment, those receiving RV/MenB co-administration had a higher chance of completing the immunization schedule and finally reaching a 95 % coverage. In 2020, about 50 % of children living in Campania Region received RV and MenB vaccines together, as a consequence of a specific indication released by the Regional Health authority. Notably, only 5 % of children receiving RV/MenB co-administration did not complete the RV vaccination schedule.

In our population we observed that children receiving RV1 had a higher chance to complete RV vaccination schedule compared to those receiving RV5. However, this finding may be partially affected by a considerable difference in the distribution of the two vaccines in the regional territory and by the distinct barriers that hamper vaccine uptake in different areas of the region. Considering that only 7 % of children living in Campania received RV1, the difference in vaccine uptake observed in our population should be taken with caution.

The impact of choosing a two or three-doses schedule on RV vaccine coverage is unclear. In Europe, some countries reported difference in vaccine uptake according to single products and schedule [18], bur others, such as Portugal that demonstrated a very high vaccination uptake, reported comparable coverage when stratifying data according to vaccine brand [21]. Similarly, there is a evidence (i.e. Austria, Latvia, Estonia) that a switch from a two- to three-dose calendar did not have an impact on overall RV vaccination coverage, suggesting that product may have a minor impact on vaccination coverage when vaccination strategies are appropriately implemented [21–24]. Data released by the Italian Health Institute did not show difference in RV vaccination coverage between regions adopting a 2- or 3-doses schedule, although a specific analysis according to RV vaccine product was not performed [25].

A positive effect of MenB/RV co-administration on the overall RV vaccination rate was associated with a 30 % increase in the overall vaccination coverage. The impact of co-administration was observed in children receiving RV1, who had an additional 10–14 % increase in fully completing the schedule. However, this effect was more evident for RV5 (about 32 %), probably due to the reduction of appointments needed to complete RV5 three doses schedule.

In addition, recent evidence demonstrated that a three-dose RV5 schedule induce a significantly higher IgA seroconversion either 4 weeks after the full series or during medium term follow up (22 weeks of life) [26]. In Campania region, RV5 was the most used vaccine and its consumption increased over time. Evidence about immunogenicity, as well as awareness about local barriers to vaccine uptake should be considered while setting up the strategies for vaccine implementation.

The MenB/RV vaccine co-administration may be a key tool to increase a timely and complete RV vaccine uptake, taking advantage of a driving force of anti-meningeal immunization and the general sensitivity by people to health risks linked to meningitis compared to underscored risks of gastroenteritis [2]. However also other strategies should be identified to overcome local barriers to implementation and to enhance RV vaccine uptake.

The effects of RV/MenB vaccine co-administration on MenB vaccination coverage was not specifically addressed by the present study, however a potential (reverse) impact also on MenB uptake is likely.

The time of administration of RV vaccines and their inclusion within local NIPs, historically, are among the major barriers to implementation. Discrepancies among the recommendations provided by international agencies, national health systems and SmPC further hamper vaccine uptake. Timing, number of vaccination appointments, fear of administering an excess of antigens, hampering the immune response, increase in side effects and other effects, although not all supported by evidence, are all barriers to achieve a full immunization program. COVID-19 immunization added to this trend. The lack of specific data contributes to the fears.

We demonstrated that administering the first RV vaccine dose within the recommended timeframe increases the likelihood of completing the vaccination schedule on time. However, it should be noted that, in our population, about 18 % of children received the first dose between 12 and 15 weeks (instead of within 12 weeks as indicated by SmPC), as reported by the regional plan irrespective of type of RV vaccine. This practice had a beneficial impact on the overall RV coverage, as it allowed additional 13,660 children (accounting for about 6 % of the entire regional population) to access the RV vaccination schedule.

It should be noted that a further 6 % of children started the RV schedule even after 15 weeks of life. Likewise, a similar percentage complete the schedule late (after 24 or 32 weeks according to RV vaccine). In our population, RV5 schedule was administered in a more timely fashion for a larger proportion of children compared to RV1. This might be the consequence of a boarder period of administration allowed by the SmPC. The provision of the Regional Health Bureau to extend the administration of RV1 up to 32 weeks allowed for schedule completion in a further small percentage of children.

An extension of the age range or the possibility to provide a catch up vaccination would be possible strategies to increase the RVI coverage, although data about the safety should be carefully collected. Reassuring data from the U.S. national vaccine surveillance system did not identify an increased risk of adverse events among children aged $\geq$8 months compared to children vaccinated within the scheduled time [27]. In addition, a risk–benefit analysis conducted in low- and middle-income countries estimated that a rotavirus vaccine schedule without any age restrictions would avert an additional 136 rotavirus deaths for each excess intussusception death caused by vaccination. In other words, this meant an additional 21–25 % children who would potentially be eligible for rotavirus vaccine, and overall would lead to a net 42,800 additional lives saved [28].

Identifying, and possibly ruling out, the risk factors for delaying the schedule may be a further strategy to potentially optimize vaccination offer and immunization rate.

It is known that the recommended minimum interval between doses is 4 weeks, but in our study population the first and second doses were given more than 50 days apart. A delayed administration of doses is associated with a higher risk of delayed conclusion of RV schedule and of an incomplete vaccination.

As previously highlighted, taking advantage of the RV/MenB vaccine co-administration may be a promising strategy to increase RV immunization coverage.

In our period of observation only 34 % of children received at least the first dose of RV vaccine and among these children the rate of those who completed the schedule ranged between 83 % and 89 %. A rapid identification of children with an incomplete schedule, whose parents seem to be willing to vaccinate their children against RV, may result in a catch-up vaccination and easily increase the immunization coverage by about 17 %, according to our data.

A limit of this work is the lack of regional safety data. Studies comparing the safety of receiving vaccines alone or in co-administration

are rare and report scattered data, however, there seems to be no substantial risk of any adverse events in subjects receiving co-administration compared with separate administration of the same vaccines [29].

The occurrence of COVID-19 pandemic during the last year of the study period, is a further limit to the interpretation of our data.

We are aware that COVID-19 Pandemic had a huge, long-lasting impact on healthcare systems, and immunization programs have been similarly affected by direct and indirect consequences of SARS-CoV-2 diffusion. However, according to our data the impact has been relatively limited, also considering that a catch-up vaccination is not possible for RV vaccine that need to be administered between 6 weeks and 6 months of life [30]. The drop in RV vaccination coverage reported in some countries will likely result in an increase in new RV infection and circulation of the virus in susceptible populations [31]. During the first year of pandemic the positive trend toward increases in RV vaccination rate had a setback with a relative loss of 6 % additional coverage in comparison to what estimated by the trends based on the previous four years of observation (data not shown). The delay in RV vaccine's doses uptake did not significantly change in 2020, meaning that families that were appropriately reached by the local health services completed RVV schedule following a pathway similar to pre-pandemic years.

In conclusion, RV immunization rates are still suboptimal, however, co-administration of Rotavirus and Men-B vaccines may be an effective strategy to improve vaccination coverage, in the absence of concerning data about safety and reactogenicity. RV vaccination coverage is progressively increasing in Campania Region. However, additional strategies are needed to overcome local barriers and improve the overall vaccination rate.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Andrea Lo Vecchio reports financial support was provided by University of Naples Federico II. Andrea Lo Vecchio reports a relationship with University of Naples Federico II that includes: funding grants. The data presented in the present paper are part of the results of an Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp. obtained by the Corresponding author Andrea Lo Vecchio. The opinions expressed in this paper are those of the authors and do not represent those of Merck Sharp & Dohme Corp.

Data availability

Data will be made available on request.

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The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp & Dohme Corp.

Author Contributions

Andrea Lo Vecchio conceived the study and coordinated the project.

Andrea Lo Vecchio, Raffaele Palladino and Giuseppina Affinito analysed data.

Andrea Lo Vecchio, Sara Maria Scarano and Margherita Del Bene wrote the first draft.

Sara Maria Scarano and Margherita Del Bene developed figures and tables.

Pietro Buono and Ugo Trama had access to the Regional Vaccination Registry and provided original anonymized data about coverage and vaccine products.

Alfredo Guarino provided fundamental contribution to the study and reviewed the final draft of the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.12.003.

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