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Italian immunization calendar implementation: Time to optimize number of vaccination appointments?

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ABSTRACT

In the Italian vaccination schedule, at least six vaccination appointments are scheduled in the first year of life. This implies more discomfort for both the patient and the parents. This was particularly evident during the COVID-19 pandemic, during which several appointments were missed. A UK experience with three injectable vaccines and an oral one co-administered at the same appointment (4-in-1) at 2 and 4 months of age showed interesting results. The vaccination coverage was high, consistent with previous practice, and no relevant increase in adverse events was reported. Translating the UK experience into the Italian context would not be immediate, due to several organizational and social issues. Nevertheless, this option warrants some further considerations, which are discussed in this manuscript.

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In Italy, as in several other countries, the COVID19 pandemic has had a relevant impact in routine clinical activities including vaccination administration, as recommended by the Italian National Immunization Plan (PNPV).¹

After the implementation of compulsory vaccination scheme in 2017, in 2019 the hexavalent vaccine (Hexa) and conjugated pneumococcal vaccine (PCV) coverage in Italy exceeded 95% across the Country.² Moreover, measles-mumps-rubella-varicella vaccinations approached, for the first time in Italy, 95% of coverage, reducing the high burden of measles in 2017 (4991 cases).³ However, the COVID-19 pandemic has had a remarkable impact on overall pediatric immunization coverage.⁴ To avoid the harmful consequences of decreased coverage, in July 2020 the Ministry of Health released recommendations to underline the importance of timely vaccination and catching up on missing administrations.⁵ Furthermore, four Italian scientific societies recently published a paper underlining the value of combined vaccines and co-administrations as a tool to recover high vaccination coverage.⁶

From this perspective, several options to optimize the number of vaccination appointments during the first year of life might be worth further discussion.




Italy was the first country in Europe to introduce the so-called “2 + 1” schedule, with two doses for priming and one dose as a booster during the first year of life.⁷ Such a choice was certainly driven by both the previous national experience and the availability of new combined vaccines. Also, this choice was made with the aim of avoiding more than 2 injections during the same appointment, reducing parental stress and increasing the rate of adherence to the following appointments.⁸

In 2017 the PNPV was updated and rotavirus (RV) and Meningococcus B (4CMenB) vaccination were introduced at

the national level.¹ RV was available in oral formulations^{9,10} and was introduced in co-administration with other vaccinations (Hexa and PCV), while 4CMenB vaccination was introduced as a separate administration.^{9,10} The decision, again, was made to avoid more than two injections at a time, other than for safety reason, since 4CMenB was a recently developed vaccine and safety data collection was still ongoing.¹ After the end of the additional monitoring period and the optimization of the vaccine schedule (as 2 + 1 schedule),¹¹ 4CMenB was introduced in the routine administration, but still no more than two injections were administered.^{12,13} As a result, in the national vaccination schedule during the first year of life at least six vaccination appointments are required (Table 1).

In this regard, we have looked with interest to the UK experience carried out in the past few years (2015–2019), where, due to the introduction of the 4CMenB vaccination campaign, three injectable vaccines (pentavalent+PCV +4CMenB) and one oral (RV) were co-administered at the same appointment (4-in-1) at 2 months of age.¹⁴ The 4-in-1 strategy was suspended in 2020 because of the adoption of a new 1 + 1 schedule of PCV.¹⁵ Noteworthy, since 2015 in the UK vaccination schedule, four injectable vaccinations including a live-attenuated vaccine (Hib/MenC, PCV, Measles-Mumps-Rubella and MenB) are co-administered in children at one year of age during one single appointment.¹⁵ UK observational data revealed that the effectiveness of neither RV nor 4CMenB vaccination was affected.¹⁶ Other authors highlighted that the side effects were overall comparable, if not lower as compared to previous data.^{17,18} Some concerns arose regarding fever onset, which initially seemed to increase, leading to more hospital admissions¹⁹ and to the prophylactic use of paracetamol.²⁰ Overall, this scheme showed to be successful

Table 1. Current Italian immunization calendar in the first year of life with at least six vaccination visits to be completed.

							
	3 month	4 month	5 month	6 month	11 month	12 month	13 month
HEXA			HEXA		HEXA		MMRV
PCV			PCV		PCV		MenC
RV		MenB (RV)*	RV	MenB		MenB	

*RV 3 doses.

Legenda:

HEXA: diphtheria, tetanus, acellular pertussis, hepatitis B (HBV), inactivated poliomyelitis and Haemophilus influenzae type b (Hib).

MMRV: Measles, Mumps, Rubella, and Varicella; PCV: pneumococcal conjugate; MenC: Meningococcal C; MenB: Meningococcal B; RV: Rotavirus.

in term of vaccination coverage and consistent with that of the previous years.²¹

We are fully aware that translating the UK experience into the Italian context would not be immediate due to organizational and social issues (such as low compliance of parents). Nevertheless, this hypothesis warrants some consideration.

The 4-in-1 hypothesis during the first year of life was first made possible in the PNPV 2012–14, where the possibility of delivering more than 2 injections per appointment was considered safe and with no immunological impact.⁸

From an epidemiological point of view, the early administration of the 4CMenb is protective before the reported peak of disease in the first year of life²² and an increase in the effectiveness was recently confirmed.²³ Similarly, early completion of RV vaccination increases the number of children protected before the peak of rotavirus disease and reduces the risk of intussusception.²⁴

Moreover, one advantage of implementing the 4-in-1 hypothesis into the Italian vaccination schedule would be the reduction in the number of vaccination appointments in the first year of life, from six to three/four (depending on the RV vaccine in use) per year (Table 2). Babies born in Italy in 2019 across 20 Italian regions (420084 newborns; regional range 841–73117; regional mean 20,004)²⁵ may be used for a simulation. Assuming that ten Regions might use the two-dose RV vaccine and ten Regions the three-dose RV vaccine, adjusting to a target coverage of 95%, 950190 vaccination appointments $([(20004 \times 0.95 \times 10 \times 2) + (20004 \times 0.95 \times 10 \times 3)] = [380076 + 570114] = 950190)$ would be saved per year. Although such a result is purely indicative at a national level, because of the high variability across Regions, it is still

noteworthy. Moreover, assuming 12 minutes for each vaccination appointment,²⁴ a total of 190,038 $(950190 \times 12/60)$ working hours would be saved per year. No official data are available to quantify the economic value of such a huge number of working hours, nor it is possible to estimate the worth of avoiding loss of working hours for parents to attend vaccination appointments. However, we might speculate that these working hours could be dedicated to catch up the missed vaccinations due to the COVID-19 pandemic or to raise the vaccination coverage of missing vaccination programs like Human Papilloma Virus (HPV) or those of older age like Tdap, zoster, PCV or flu, that in Italy are far from the recommended target.^{1,26} Obviously, the 4-in-1 hypothesis would lead to fewer appointments and therefore reduced stress for both children and parents.

However, prior to a new scheme introduction, all health care professionals (HCPs) involved in the vaccination program should be appropriately trained to make them feel comfortable with the new strategy and able to reassure parents about the safety and efficacy of co-administration other than about the epidemiological advantages for children and for the parents as well. At the same time, a communication campaign should be started to inform all parents of the opportunities for the new schedule. Vaccination coverage should be even more closely monitored to prevent parental hesitancy and thus missing appointments, as well as vaccine vigilance activities should be reinforced to monitor the rate of adverse events. To address these points and generate preliminary Italian data, single Local Health Units or regional experiences of the 4-in-1 strategy implementation might be involved to design a national implementation pathway.

Table 2. Italian immunization calendar in the first year of life according to the 4-in-1 hypothesis with the reduction of the number of vaccination visits to three–four (depending on the RV vaccine in use) visits per year.

3 month	4 month	5 month	11 month	13 month
HEXA		HEXA	HEXA	MMRV
PCV		PCV	PCV	MenC
MenB		MenB	MenB	
RV	(RV)*	RV		

*RV 3 doses.

Legenda:

HEXA: diphtheria, tetanus, acellular pertussis, hepatitis B (HBV), inactivated poliomyelitis and Haemophilus influenzae type b (Hib); MMRV: Measles, Mumps, Rubella, and Varicella; PCV: pneumococcal conjugate; MenC: Meningococcal C; MenB: Meningococcal B; RV: Rotavirus.

In conclusion, the 4-in-1 strategy would request efforts to secure its implementation without negatively impacting on vaccination coverage; however, it would generate epidemiological and organizational improvements that could be beneficial either for the population and also for the Health Care System.

Disclosure statement

Dr. Poscia, Dr. Lo Giudice, Dr. Nigri, Dr Perone, Dr Russo and Prof Agosti declare that the topic presented here was initially discussed during an Advisory Board arranged by GSK, for which they received a grant. Dr. Bresesti has no conflict of interest to disclose and received no funding from GSK nor other public or private funding

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