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Discordant immunization schedules can complicate vaccine evaluation for Europe

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Abstract

Background: Most of the world's vaccines are produced in Europe. Although vaccine licensure can be centralized through the EMEA, immunization recommendations are established at the national levels, reimbursement policies vary widely (ranging from regional to national, from private to public) and the lag time can be long between licensure and eventual introduction into a national immunization program.

Methods: An example of this discordance is the paediatric combination vaccines. Young infants in some EU countries receive a whole-cell pertussis vaccine, in a three- to five-vaccine combination ("DTPw | IPV | Hib"). Acellular pertussis vaccines have been introduced over the last decade in many other EU countries, with four- to six-vaccine combinations ("DTPa | IPV | HBV | Hib"). Either of these combinations may be administered with a "3 + 1" schedule, with the first dose given between the age of 2 to 3 months, a spacing of 1 to 2 months between doses, and the final (booster) dose usually given at anywhere between 12 and 24 months of age, but in a handful of countries as late as the age of 3 to 5 years. By contrast, a "2 + 1" schedule is applied in some countries for the "DTPa | IPV | Hib" or "DTPa | IPV | HBV | Hib" vaccines: first dose, 3 months old; spacing, 2 months between doses; final (booster) dose, 11 to 14 months of age.

Results: Differing national policies in the EU may have led to delays in the introduction of the newest vaccines (e.g., pneumococcal conjugate, meningococcal conjugate, rotavirus, influenza, varicella-zoster, etc.) that must be shown to be compatible with the various infant immunization programs across Europe. This could delay the likelihood, in some EU countries, of the public health advancements that these new vaccines can provide.

Conclusions: Sharing of best practices from vaccination schedules might rationalize vaccine development, streamline the introduction of novel vaccines into the national immunization programs, and facilitate the evaluation of the impact of new vaccines in Europe.

Key words: European Union, immunization programs, pneumococcal vaccines, rotavirus vaccines, papillomavirus vaccines

The "European Vaccine Manufacturers" (EVM)

Vaccines are a strategic, knowledge-based industry for Europe. The "European Vaccine Manufacturers" (EVM) [http://www.evm-vaccines.org/], founded in 1991, has as members the major worldwide vaccine producers: Baxter, Berna (Crucell), GlaxoSmithkline, MedImmune, Novartis Vaccines, Sanofi Pasteur, Sanofi Pasteur MSD, Solvay and Wyeth. The characteristics of the EVM members include the highest research and development (R&D) intensity in Europe, a strong industrial infrastructure in Europe, and the development of vaccines for "Developed" and "Developing" countries [1].

Vaccine R&D encompasses four major areas [2]: infectious diseases (pathogens / pathogenesis, and epidemiologic surveillance), vaccines candidates (safety and immunogenicity profile, and extensive clinical evaluations), licensure / recommendations (schedules, risk-benefit, and pharmacoeconomics) and production (Good Manufacturing Practices, lot release, and demand forecasts). In the present paper, attention will be focused on "licensure / recommendations".

Discordant infant vaccination schedules across the EU

Introduction of vaccines in Europe is complicated by the discordant infant vaccination schedules across the EU. Although European licensure is centralised through the European Medicines Agency (EMEA) [3], recommendations

are established at the national levels [4]. Reimbursement policies vary widely, ranging from regional to national, from private to public [5]. Consequently, the lag time can be long between licensure and introduction into a national immunisation programme.

Pertussis-based paediatric combination vaccines are taken as an example [6] of discordant vaccination schedules across the EU. These paediatric combination vaccines protect European children against tetanus (T), diphtheria (D), whooping cough (P), poliomyelitis (IPV), bacterial meningitis (Hib), and hepatitis B (HBV). Each new paediatric vaccine must be compatible with the various infant immunisation schedules in place across Europe by age at first dose and

Table 1. Acellular pertussis combination vaccines.

Acellular pertussis combination vaccines				
First dose, age (months)	**Spacing (months)**	**Booster dose, age (months)**	**Country**	**Pediatric combo**
"3 + 1" schedules				
2 mo	1 mo	11 mo	**Netherlands**	Five-vaccine
		11 to 14 mo	**Germany**	Six-vaccine
		12 mo	**Luxembourg**	Six-vaccine
		13 to 18 mo	**Belgium**	Six-vaccine
		16 to 18 mo	**France**	Five-vaccine
		18 mo	**Hungary**	Five-vaccine
		36 to 60 mo	**UK**	Five-vaccine
	2 mo	10 mo	**Slovak Republic**	Five-vaccine
		15 to 18 mo	**Spain**	Six-vaccine
		18 mo	**Greece**	Five-vaccine
		18 mo	**Portugal**	Five-vaccine
		48 to 60 mo	**Ireland**	Five-vaccine
3 mo	1 mo	11 to 24 mo	**Austria**	Six-vaccine
		12 to 24 mo	**Slovenia**	Four-vaccine
	1½ mo	18 mo	**Latvia**	Five-vaccine
"2 + 1" schedules				
3 mo	2 mo	11 to 14 mo	**Italy**	Six-vaccine
		12 mo	**Denmark**	Five-vaccine
			Finland	Five-vaccine
			Sweden	Five-vaccine

Source: VENICE Project, see the "Vaccines and Immunisation Newsletter" of the European Centre for Disease Prevention and Control, http://ecdc.europa.eu/]

Table 2. Whole cell pertussis combination vaccines.

Whole cell pertussis combination vaccines				
First dose, age	**Spacing**	**Booster dose, age**	**Country**	**Pediatric combo**
"3 + 1" schedules				
2 mo	1-mo	12 to 18 mo	**Malta**	Three-vaccine
		24 mo	**Bulgaria**	Three-vaccine
	1½-mo	16 to 18 mo	**Poland**	Four-vaccine
	2-mo	12 mo	**Romania**	Three-vaccine
		18 mo	**Lithuania**	Five-vaccine
2.5 mo	1-mo	18 to 20 mo	**Czech Republic**	Four-vaccine
	2-mo	12 to 20 mo	**Cyprus**	Three-vaccine
3 mo	1½-mo	24 mo	**Estonia**	Three-vaccine

Source: VENICE Project, see the "Vaccines and Immunisation Newsletter" of the European Centre for Disease Prevention and Control, http://ecdc.europa.eu/]

spacing between each primary dose, association with other new vaccines (pneumococcal conjugate, meningococcal conjugate, rotavirus, influenza, varicella, etc.), and number of primary series doses ("2+1" and "3+1").

Acellular pertussis vaccines have been introduced over the last decade in many EU countries, based on four- to six-vaccine combinations: DTPa | Hib | IPV | HBV (Table 1). In some EU countries (Bulgaria, Cyprus, Czech Republic, Estonia, Lithuania, Malta, Poland, and Romania), young infants receive the whole-cell pertussis vaccine: three-vaccine combinations (DTPw), four-vaccine combinations (DTPw | Hib), or five-vaccine combinations (DTPw | IPV | Hib) (Table 2).

As a consequence of the diversity of paediatric combination vaccine schedules, each new paediatric vaccine (e.g., pneumococcal conjugate, meningococcal conjugate, rotavirus, influenza, varicella, etc.) must be compatible with the various infant immunisation schedules in place across Europe:

- "3+1" and "2+1" schedules
- Two-month and one-month spacing between each primary dose
- Whole cell and acellular pertussis combination vaccines
- Pediatric combinations that contain four, five or six different vaccines

New vaccines from investment in innovation

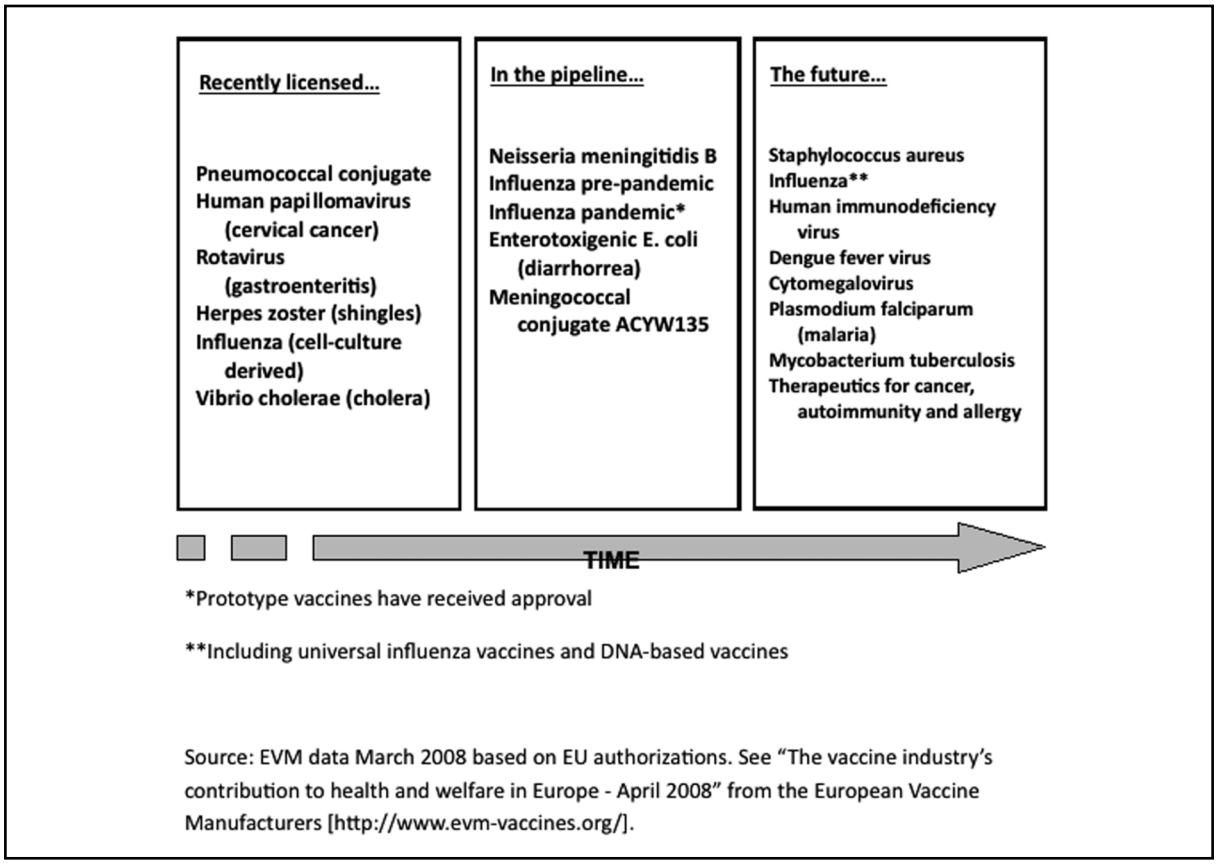
The EVM members have recently licensed a number of new vaccines; there are vaccines "in the pipeline"; and a number of other diseases are being targeted for vaccination in the future (Figure 1) [7].

Once licensed, every new vaccine has a long way to go before reaching the population. In order to have a full understanding of the time needed to gain full access to a new vaccine, one must include the time necessary for European authorization, for national recommendations, and for national funding. Recently-licensed vaccines have high potential to reduce disease:

- Pneumococcal disease in infants and toddlers (EU authorisation 02/2001) [8]
- Rotavirus gastroenteritis in infants and toddlers (EU authorisation 02/2006) [9]
- Human papillomavirus infections in adolescent girls and women (EU authorisation 09/2006) [10]

Nonetheless, the time for access to these new vaccines can be long (Figure 2). This delay means that there is a significant difference, in terms of use of the new vaccines, between the countries of

Figure 1. New vaccines from investment in innovation.



Europe (Figure 3). Furthermore, these delays might eventually make Europe less attractive for future vaccine research and development.

How to improve equity of access to new vaccines?

The industry proposal is to evaluate early and evaluate fully at the country level. In the current linear system, completion of European authorization can lead to national recommendations that may then lead to national funding, each one following the other in a stepwise manner. In its place, it could be possible for national recommendations to be composed while European authorization is under review, and likewise for national funding analyses to begin as the national recommendations are being prepared, thereby compressing the time until full access to a new vaccine.

Conclusion

Most of the world's vaccines are produced in Europe. Nonetheless, differing country policies for immunisation in the European Union have led to delays in the introduction of the newest vaccines that must be shown to be compatible with the different infant immunization programs across Europe, and then after European authorization - in a stepwise manner - receive national recommendations and then undergo national funding analyses. Taken together, these lower the likelihood, in some EU countries, of the public health advancements that these new vaccines can provide.

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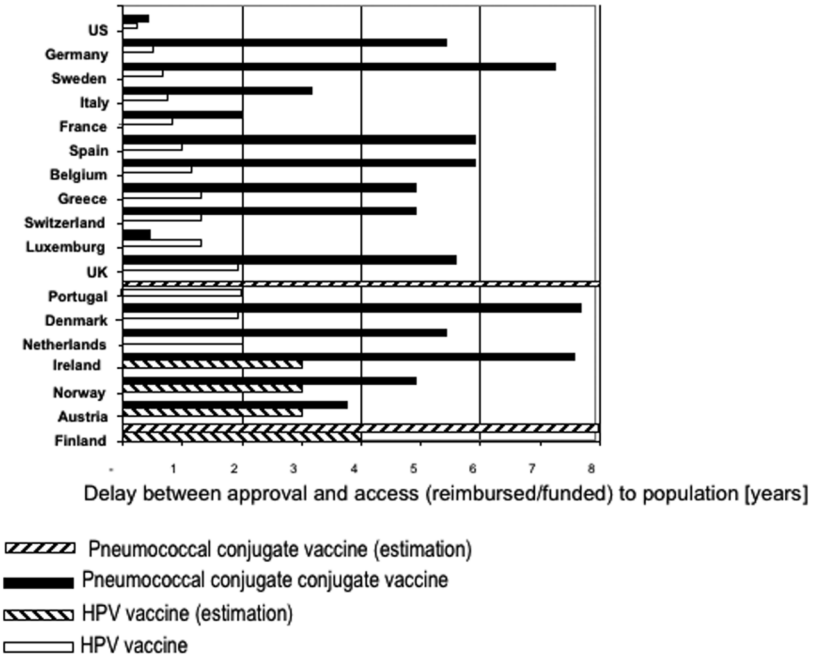
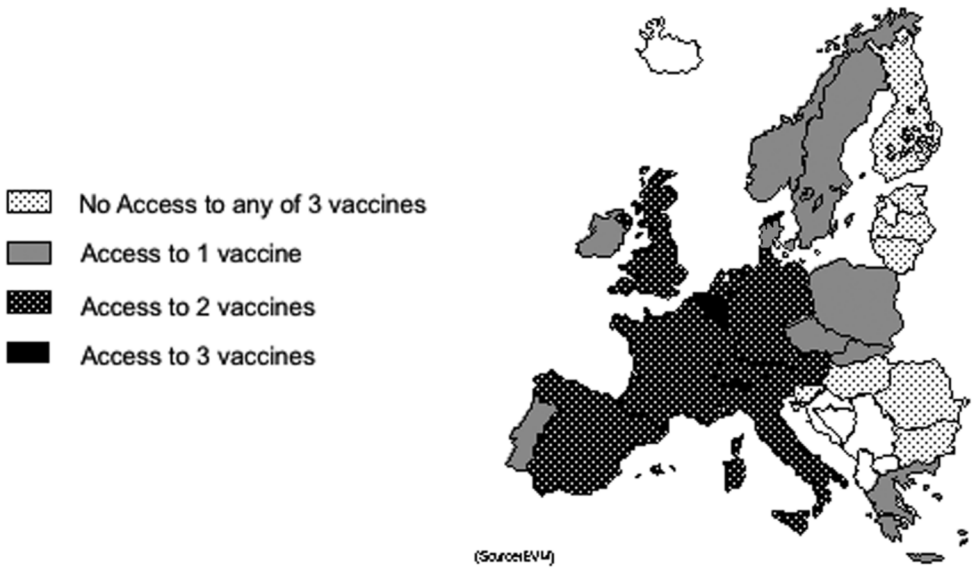
Figure 2. Delay between approval and access for the pneumococcal conjugate and the HPV vaccines.



Updated September 2008, based on data concerning Pneumococcal and HPV vaccines.
Access is defined by the existence of a Recommendation AND Funding. N.B., The figure does not make the distinction between National / Regional recommendation and reimbursement, or General / Specific recommendation and reimbursement.
Sources: the "Vaccines and Immunisation Newsletter" of the European Centre for Disease Prevention and Control [http://ecdc.europa.eu/], the "National Childhood Vaccination Schedules" at EUVAC.NET [http://www.euvac.net/] and information provided by the members of the EVM.

Figure 3. There is a significant difference in vaccines in terms of use.



Updated September 2008. Based on data concerning Pneumococcal, HPV and Rotavirus vaccines. Access is defined by the existence of a Recommendation AND Funding.
N.B., The map does not make the distinction between National / Regional recommendation and reimbursement, or General / Specific recommendation and reimbursement

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