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PERSPECTIVE

Vaccines administered simultaneously: directions for new combination vaccines based on an historical review of the literature

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Summary

Objectives: The recognized benefits of administering vaccines simultaneously has encouraged vaccine producers to develop combination vaccines. If contemporary research and development can realize vaccines that achieve the current standards for safety, immunogenicity, and efficacy, other specific vaccine associations may also merit reconsideration as combination vaccines.
Methods: An historical review of the vaccine association literature reveals two important themes: first, the programs of mass vaccination, in particular, the eradication of smallpox, sessions where multiple vaccines (other than the smallpox vaccine) were given concurrently, and the Expanded Programme on Immunization (EPI); and, second, the domain of travel vaccines, including travellers to a disease-endemic country (such as migrants, tourists, military personnel, or expatriates) and WHO requirements for international travellers.
Results/conclusions: Based on this historical review, combination vaccines worth reconsideration could fill epidemiologic niches in the EPI with, for instance, a measles–yellow fever, a measles–Japanese encephalitis or a pertussis-based paediatric combination rabies vaccine. Furthermore, other combinations could broaden protection against the pathogens responsible for meningitis, pneumonia, or enteric

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diseases. Nevertheless, complex issues such as necessity, feasibility, or affordability will ultimately determine if any one of these becomes a combination vaccine.

Objectives

In the simultaneous administration of associated vaccines, a person receives two or more vaccines at the same time, usually in different anatomic sites. Although this frequently requires additional injections,[1] parents often strive to keep their family's immunizations up to date, even if this means taking their children to numerous vaccination sessions.[2] Likewise, a person travelling to a disease-endemic area may accept multiple injections in order to reside under the best possible circumstances.[3]

Besides the need for multiple administrations, another issue for vaccine associations is the possibility of interactions between the immune responses.[4] In the best case, association enriches the immune response which may enhance the protective efficacy. This occurs, for instance, with the simultaneous administration of the inactive and the live forms of the poliovirus vaccines,[5] and this phenomenon has also been reported during the clinical development of influenza virus vaccines.[6,7] In the worse case, however, a vaccine in association with another displays poorer immunogenicity than the same vaccine administered alone. When associating live virus vaccines, studies recommend that there be an interval of 30 days between the different vaccines to limit any possible interference.[8]

Immunization against different transmissible diseases through simultaneous injections during the same vaccination session began in the 1930s.[9,10] Subsequently there has been important vaccine research and development allowing health authorities to continue to enlarge the list of vaccine-preventable diseases. Many of these newly licensed vaccines have found a place in established immunization schedules and new vaccines continue to appear for consideration by paediatric vaccination programs, both in industrialized and in developing countries.[11,12] In industrialized countries new vaccine arrivals have included the hepatitis A virus vaccine, the rotavirus vaccine, the varicella-zoster virus (VZV) vaccine, the *Streptococcus pneumoniae* capsular polysaccharide (CPS)—carrier protein conjugate vaccine, and the *Neisseria meningitidis* serogroup C CPS—carrier protein conjugate vaccine. Furthermore, combinations of the measles virus vaccine with a rubella virus or a mumps virus vaccine are commonly used in industrialized countries, and are becoming routine in some developing countries.[13,14]

In the developing world, the Global Alliance for Vaccines and Immunization (GAVI) strives to vaccinate children against multiple infectious agents during a few vaccination sessions, in fostering the work of the Expanded Programme on Immunization (EPI).[15] Through the EPI, clinical trials or demonstration programs are performed to introduce vaccines, including those against invasive *Haemophilus influenzae* type b (Hib) disease,[16,17] Japanese encephalitis (JEV),[18] yellow fever,[19] invasive *N. meningitidis* disease,[20] or rabies,[21] into local programs according to specific epidemiological concerns. In the absence of appropriate combination vaccines, these introductions add new injections to the immunization schedule and may add new sessions to the vaccination program.

The combination vaccines that are currently available were first introduced as simultaneously administered individual vaccines. The person administering an extemporaneous combination vaccine mixes the different vaccine valences, either in the same syringe (e.g. the by-pass syringe) or in the same vial, just before injection. In contrast to an association of different vaccines, a combination vaccine is a single product. Combination or extemporaneous combination vaccines benefit from regulatory approval only upon completion of a full program of pharmaceutical and clinical development.[22]

The purpose of this paper is to review the vaccine association literature from an historical perspective to suggest potential combination vaccines that, in the light of current vaccine technology, might merit reconsideration.

Materials and methods

The electronic database Medline from 1966 to 2003 was searched using the keywords 'vaccination' (or 'immunization') and 'association' (or 'simultaneous', or 'concomitant'). From over 2000 references initially obtained, the focus was narrowed to public health programs with established vaccines (i.e. clinical trials or demonstration projects). Vaccine associations were excluded if they had

Table 1 Important themes in the vaccine association literature.

Programs of mass vaccination	The eradication of smallpox Sessions where multiple vaccines (other than smallpox vaccine) were given concurrently The Expanded Programme on Immunization
Travel vaccines	Travellers to a disease-endemic country (such as migrants, tourists, military personnel, or expatriates) WHO requirements for international travellers

subsequently become licensed vaccines, for example, the paediatric combinations that were initially based on diphtheria toxoid and tetanus toxoid—whole-cell *Bordetella pertussis* vaccine (DTwcP). A hand search of the reference list of each article obtained was also conducted.

Results

Vaccinology is rich in examples of clinical trials and of field studies of simultaneous immunizations against multiple infectious pathogens.[23] As noted in Table 1 it may be helpful to sub-divide the vaccine association literature into two groups: the programs of mass vaccination and travel vaccines. These programs of mass vaccination describe situations ranging from the eradication of smallpox to the EPI vaccination sessions. The domain of travel vaccines encourages vaccine associations to provide optimal protection to travellers to a disease-endemic region, which might include migrants, tourists, military personnel, or expatriates.

The programs of mass vaccination

The eradication of smallpox

During the campaign that eradicated smallpox, public health workers intensively targeted all age groups for vaccinia vaccine immunization. Furthermore, the vaccinia vaccine was administered concurrently with paediatric vaccines like DTwcP, the oral poliovirus (OPV) vaccine, the BCG vaccine against tuberculosis, or the measles virus vaccine.[24–26] Children in Nigeria, for instance, received a smallpox vaccine, a DTwcP vaccine, a measles virus vaccine, and a yellow fever virus vaccine simultaneously.[27] The vaccinia vaccine also was given concomitantly with vaccines matched to a local epidemiology, like the yellow fever virus vaccine[28,29] or measles virus vaccine.[30,31] Children vaccinated against smallpox under field conditions of mass vaccination in Africa received simultaneous immunizations against both measles and against yellow fever.[32,33]. Furthermore, investigators in the former Soviet Union reported giving the smallpox vaccine in association with vaccines against plague, tick-borne encephalitis (TBE), tularaemia, or typhus.[34] Russian military recruits received concomitant tuberculosis, smallpox, typhoid fever, and tetanus vaccines.[35]

Sessions where multiple vaccines (other than smallpox vaccine) are given concurrently

There have been programs of mass vaccination on the African continent[36] and in the former Soviet Union,[37] where multiple vaccines were administered concurrently. For instance, a group of Nigerian children received four vaccines by association: the OPV vaccine, the measles virus vaccine, the *N. meningitidis* serogroups A and C polysaccharide (Men A/C PS) vaccine, and a killed, whole-cell *S. typhi* vaccine.[38] In similar circumstances, children in Sudan received the BCG vaccine in association with a combination vaccine that had been mixed just before injection and contained the measles virus vaccine, diphtheria toxoid and tetanus toxoid, the inactivated poliovirus (IPV) vaccine, and the Men A/C PS vaccine.[36] A paper from investigators in the former Soviet Union describes the concomitant administration of a *S. typhi* toxoid vaccine ('TABTe', tetravalent tetanus, typhoid, and paratyphoid A and B) with immunizations against TBE, smallpox, tularaemia, influenza, and tuberculosis.[39] Another publication documented the concurrent administration of the whole-cell *S. typhi* vaccine, with the *N. meningitidis* serogroup A polysaccharide (Men A PS) vaccine (mixed with diphtheria toxoid), normal human immune globulin (for hepatitis A prophylaxis), and a vaccine against influenza.[37]

The Expanded Programme on Immunization (EPI)

The 27th World Health Assembly established the EPI in Geneva in 1974 aiming to protect children against potentially mortal infectious diseases of childhood through immunization in infancy with BCG, OPV, and DTwcP vaccines.[40] The EPI added the hepatitis B virus (HBV) vaccine in 1992. Vaccination sessions are scheduled at birth and then at the ages of 6, 10, and

Table 2 Vaccine associations investigated within the Expanded Programme on Immunization.

	Measles virus	Hepatitis B virus	Measles virus + hepatitis B virus	Other EPI vaccine targets
Japanese encephalitis virus	Tseng, 1999[70]	N.D.	Yuan, 1989[69]	Intralawan, 1991[18]; Rojanasuphot, 1992[98]
Yellow fever virus	Lhuilier, 1989[65]; Mouchon, 1990[67]; Soula, 1991[68]; Coursaget, 1995[99]; Adu, 1996[66]; Stefano, 1999[64]	Yvonnet, 1986[100]; Yvonnet, 1986[101]	Coursaget, 1995[99]	N.D.
Rabies virus	N.D.	N.D.	N.D.	Lang, 1997[60,a]
Neisseria meningitidis, serogroup A or C	Ajjan, 1978[81]; Lapeyssonnie, 1979[102]; Greenwood, 1981a[82]; Omer, 1986[36]	N.D.	N.D.	Omer, 1986[36]; Yuan, 1990[103,b]

N.D. none described.
[a] DTwcP-IPV vaccine, proposed for the primary series vaccination against childhood infections.
[b] BCG vaccine against tuberculosis.
NB, a vaccine association for measles, meningococcal meningitis A, and tetanus has been demonstrated, Greenwood, 1981a[82] & Lapeyssonie, 1979[102], as well as a vaccine association to prevent hepatitis B, yellow fever, and poliomyelitis, Coursaget, 1995[99].

14 weeks. Furthermore, infants receive the measles virus vaccine when they reach nine months of age, often in association with the yellow fever virus vaccine. This has been incorporated since the inclusion of this vaccine in 1988 into the EPI of yellow fever-endemic areas of South America and Africa.

Beginning in the 1970s, investigators in the developing world explored novel associations or even combinations of EPI vaccines (Table 2). For instance, some replaced OPV with IPV, and a DTwcP—IPV combination vaccine was tested.[41,42] Attempts were made to administer, during the primary series, the DTwcP vaccine or the candidate DTwcP—IPV vaccine concomitantly with the measles virus vaccine.[43—48] But this association was ultimately abandoned. Children needed to be vaccinated against diphtheria, tetanus, and pertussis at the youngest possible age, but the immunogenicity of the measles virus vaccine tended to be poor in children vaccinated before at least nine months of age, in part due to remaining maternal antibodies.

Clinical studies in the early 1990s associated the measles virus vaccine (or the measles-mumps-

Table 3 Vaccine associations based on yellow fever virus, *Salmonella typhi*, or hepatitis A virus vaccine, intended for travellers to a disease-endemic country (e.g. migrants, tourists, military personnel, or expatriates).

	Yellow fever virus	*Salmonella typhi*	Hepatitis A virus
Salmonella typhi	Ambrosch, 1991[112]; Gapochko, 1991[34]; Ambrosch, 1994[113]	—	—
Hepatitis A virus	Receveur, 1993[108]; Bienzle, 1996[104]; Gil, 1996[109]; Dumas, 1997[110]; Bovier, 1999[111]; Bock, 2000[107]	Bienzle, 1996[104]; Vodopija, 1997[105]; Van Hoecke, 1998[106]; Bock, 2000[107]	—
Japanese encephalitis virus	N.D.	N.D.	Bock, 2000[107]
Rabies virus	N.D.	Fritzell, 1992[114]	Bock, 2000[107]
Neisseria meningitidis, serogroup A or C	N.D.	Khoo, 1995[115]	N.D.
Tick-borne encephalitis virus	N.D.	Gapochko, 1991[34]	N.D.
Vibrio cholerae	N.D.	Kollaritsch, 1996[116]	Bienzle, 1996[104]

N.D. none described; NB, a vaccine association for hepatitis A, typhoid fever, and yellow fever has been demonstrated, Dumas, 1997[110].

Table 4 Vaccine associations intended for travellers to a disease-endemic country (e.g. migrants, tourists, military personnel, or expatriates), which have been administered simultaneously with adult booster vaccine targets (e.g. diphtheria and tetanus, poliomyelitis, or influenza).

	Diphtheria/tetanus[a]	Poliomyelitis	Diphtheria/tetanus/ poliomyelitis	Influenza
Yellow fever virus	Wolga, 1986[117]; Philipps, 1996[118]	Wolga, 1986[117]	N.D.	Goullin, 1993[119]
Hepatitis A virus	Bock, 2000[107]	Bock, 2000[107]	N.D.	N.D.
Salmonella typhi	N.D.	Clasener, 1967[120]; Drabo, 1996[121]; Nejmi, 1997[122]	Petterschmitt, 1991[123]	N.D.
Tick-borne encephalitis virus	Schabet, 1989[124]	N.D.	N.D.	N.D.

N.D. none described.
[a] Diphtheria/tetanus refers to diphtheria toxoid and tetanus toxoid given individually, in association, or by combination.
NB, a vaccine association for typhoid fever, cholera, and poliomyelitis has been demonstrated, Kollaritsch, 1996[116].

rubella vaccine) with the hepatitis B virus vaccine in childhood.[49–51]

Travel vaccines

Travellers to a disease-endemic country (including migrants, tourists, military personnel, or expatriates)

Anyone entering a region endemic for a vaccine-preventable disease often quickly needs to update their immunization record.[52,53] Consequently, the immunization of travellers is an active arena for concomitant vaccinations. Judging from the studies appearing in the vaccine literature, three pairs of vaccine associations predominate for pre-travel vaccinations: the hepatitis A vaccine plus the yellow fever vaccine, the hepatitis A vaccine plus one of the *S. typhi* vaccines, or the yellow fever vaccine plus a *S. typhi* vaccine (Table 3). The hepatitis A vaccine has also been given concomitantly with vaccines against other possible travellers' diseases, such as Japanese encephalitis, rabies, or cholera (Table 3). Likewise, typhoid fever vaccines have been administered simultaneously with vaccines against rabies, invasive meningococcal disease (serogroups A and C), tick-borne encephalitis, or cholera (Table 3).

The former Soviet Union tested binary associations of vaccines for diseases as varied as TBE, typhus, plague, typhoid fever, or yellow fever.[34,39,54]

Travel vaccinations also complete a traveller's standard adult booster schedule with diphtheria toxoid and tetanus toxoid inoculations, with IPV vaccine, or with an influenza virus vaccine (Table 4).[55] Once again, the yellow fever virus

Table 5 Some vaccine indications that could drive development of new combination vaccines, within the Expanded Programme on Immunization or within industrialized country vaccination programs.

Indications	Region	Examples of possible combination vaccines
EPI vaccine targets plus rabies	EPI — selected countries of Africa, Asia and South America	Diphtheria and tetanus toxoids—*B. pertussis* vaccine—hepatitis B virus vaccine—rabies virus vaccine
Bacterial meningitis or bacterial pneumonia	Both EPI and industrialized countries	*H. influenzae* type b CPS conjugate vaccine—*N. meningitidis* CPS-carrier protein conjugate vaccine—*S. pneumoniae* CPS conjugate vaccine
Measles plus yellow fever	EPI — selected countries of Africa and South America	Measles virus vaccine—yellow fever virus vaccine
Measles plus Japanese encephalitis[a]	EPI — selected countries of Asia	Measles virus vaccine—Japanese encephalitis virus vaccine
Enteric pathogen infections	Both EPI and industrialized countries	*S. typhi* vaccine—*V. cholerae* vaccine Hepatitis A virus vaccine—*S. typhi* vaccine

[a] Each as live attenuated virus vaccines.

vaccine, the *S. typhi* vaccine, or the hepatitis A virus vaccine has been the most commonly tested association with these standard adult booster vaccines.

WHO requirements for international travellers
The WHO International Health Regulations for international travellers have included vaccinations against yellow fever or against cholera.[56,57] The only formal contra-indication to associated immunizations had been the simultaneous injections of a killed, whole-cell *V. cholerae* vaccine with a live attenuated yellow fever virus vaccine because the immune response to yellow fever appeared to be suppressed.[56,58] Although these initial claims for interference have not been substantiated,[59] the WHO no longer recommends the killed, whole-cell *V. cholerae* vaccines and they are seldom used.

Discussion

Specific vaccine associations that should drive the development of future combination vaccines

Based on the vaccine associations that appeared in the literature, five sets of vaccine associations might drive the development of future combination vaccines (Table 5):

- EPI vaccine targets plus rabies;
- bacterial meningitis or bacterial pneumonia;
- measles plus yellow fever;
- measles plus Japanese encephalitis; or
- enteric pathogen infections.

EPI vaccine targets plus rabies
In Asia investigators gave the rabies virus vaccine concurrently with a paediatric combination, DTwcP—IPV, in order to protect children against rabies before the age they would begin to walk and might become the target of animal bites.[60]

Bacterial meningitis or bacterial pneumonia
Many investigators have attempted to prevent bacterial meningitis or bacterial pneumonia in at-risk populations by the association of appropriate vaccines. For instance, some have combined the CPS—carrier protein conjugate vaccine for Hib with the CPS vaccines for *N. meningitidis* serogroup A + C and for *S. pneumoniae* (23 serotypes) in a single injection.[61] Subsequent CPS—carrier protein conjugation technology has produced new paediatric vaccines like the *N. meningitidis* serogroup C conjugate vaccine and the 7-valent *S. pneumoniae* conjugate vaccine.[62] As vaccine associations of the past are often forerunners of combination vaccines of the future, work is now underway to protect children against multiple bacterial causes of invasive disease by combining different CPS-carrier protein conjugate vaccines.

Measles plus yellow fever
The measles virus vaccine was frequently given in association with the yellow fever virus vaccine for children in vaccination campaigns conducted in Africa in the 1980s and the 1990s.[63—66] The introduction of a measles virus vaccine—yellow fever virus vaccine combination into the EPI at nine months of age, which had undergone extensive clinical development during several years until it was discontinued, seems worth reviving.[65—67]

Measles plus Japanese encephalitis
The Japanese encephalitis virus (JEV) vaccine also has been associated with the vaccines of the EPI, and in particular with the measles (or the measles-mumps-rubella) vaccine.[18,69,70] Mirroring the imperative for a measles virus—yellow fever virus vaccine combination for Africa and Latin America, the EPI in Asia might welcome a combination against measles and Japanese encephalitis, with each as a live attenuated virus vaccine.

Enteric pathogen infections
Hepatitis A virus vaccine—*S. typhi* Vi polysaccharide vaccine combinations have recently been developed.[71,72] The cholera vaccine and typhoid vaccine association continues to be explored in the guise of live attenuated vaccine candidates.[73,74]

Specific vaccine associations that are unlikely to become combination vaccines

By contrast it seems doubtful that three other sets of vaccine associations will lead to the development of combination vaccines:

- measles plus EPI vaccine targets (other than yellow fever);
- measles plus invasive meningococcal disease; or
- influenza plus pneumococcal pneumonia.

Measles plus EPI vaccine targets (other than yellow fever)
For hepatitis B endemic regions it is essential to initiate hepatitis B vaccination at birth.[75,76] A slight possibility remains that a measles—hepatitis B combination vaccine could be used for the hepatitis

B booster vaccination at nine months of age. On the other hand, it is unlikely that a combination DTwcP—measles vaccine to be given at the nine-month-old visit could be developed for the EPI.[77—80]

Measles plus invasive meningococcal disease

In Africa a simultaneous measles and meningococcal meningitis vaccination has been attempted, especially during epidemics due to *N. meningitidis* serogroup A.[81,82] By contrast, the recently developed *N. meningitidis* serogroup C CPS—carrier protein conjugate vaccine is effective when administered before the age of the recommended measles virus vaccination, so the meningococcal meningitis vaccination has already entered the primary series immunization schedule for children of some industrialized countries.[83] Furthermore, quadrivalent *N. meningitidis* CPS—carrier protein conjugate vaccines (serogroups A, C, W-135, and Y) and meningococcal serogroup B vaccines are under development.[62] Consequently, a *N. meningitidis*—measles virus vaccine combination is unlikely to be developed.

Influenza plus pneumococcal pneumonia

Among elderly populations, *S. pneumoniae* superinfections pose a particularly risky sequel to an influenza virus infection. Hence, clinicians and geriatric medical specialists have advocated the association of the influenza virus vaccine with a *S. pneumoniae* capsular polysaccharide vaccine (23 serotypes) among at-risk populations.[84,85] The current scheduling of these two vaccinations, which is yearly for the influenza vaccine but might be five to ten years later for a second pneumococcal pneumonia vaccination, would seem to preclude development of a manageable combination vaccine.[86]

Conclusions

The pace of vaccine research and development continues unabated leaving health authorities with the welcome dilemma of introducing novel vaccines to already full vaccination schedules. Consequently, some health authorities have responded to the infectious disease epidemiology within their region by including new vaccines in their immunization schedules. Examples from the EPI are universal vaccination programs against invasive Hib disease and regional programs against yellow fever or Japanese encephalitis. Some countries in Asia have adopted Japanese encephalitis virus vaccination during childhood, and this practice may expand.[87]

Likewise, some industrialized countries have recently added the hepatitis A virus vaccine, the VZV vaccine, or the *S. pneumoniae* CPS—conjugate vaccine to paediatric immunization schedules. In addition, children in other industrialized countries now routinely receive a *N. meningitidis* serogroup C CPS—carrier protein conjugate vaccine,[83] and paediatric vaccination schedules throughout the world might eventually include immunization against the prevalent serogroups of *N. meningitidis*.[88]

Handling the inevitably complex assortment of novel vaccine associations requires inventiveness. Accordingly, efforts intensify to streamline the vaccination calendar. As noted, the industrialized world tends to simplify paediatric immunization schedules by replacing associations of different vaccines with combination vaccines.[89,90] For instance, children may receive a five- or a six-component paediatric vaccine that combines DTP (whole-cell or acellular pertussis), IPV, HBV, and Hib vaccines (e.g. DTP—IPV—HBV, DTP—IPV—Hib, or DPT—IPV—HBV—Hib).[91,92]

There are other approaches to dealing with new vaccine associations, which include accelerated vaccination schedules, intercalation of new vaccination visits between established immunization sessions, dropping a vaccine dose from an established schedule, or substituting non-parenteral modes of administration to replace the customary injection(s). Ultimately, the goal of the EPI remains an association of vaccines given by mouth during early infancy to confer lifelong protection.[93,94]

This review of the literature on concomitant immunizations, which is based on historical and public health perspectives, suggests that some possible combination vaccines deserve reconsideration (Table 5). Of note, regional or international health authorities charged with serving the health needs of children in developing countries might find any of the following attractive:

- a measles virus vaccine—Japanese encephalitis virus combination vaccine (for children in affected regions of Asia);
- a measles virus vaccine—yellow fever virus combination vaccine (for infants in affected regions of Latin America and Africa); or
- a DTwcP-IPV—rabies virus combination vaccine (for infants in affected regions worldwide).

Since the Hib vaccine is being added to the DTP-based paediatric combination vaccines, any paediatric immunization program might increase the need to integrate other bacterial meningitis/bacterial pneumonia vaccines based on capsular polysaccharide-carrier protein conjugate vaccines such as those against *S. pneumoniae* (at least 7 serotypes) and against *N. meningitidis* (ultimately, serogroups A, C, W-135, and Y).

Despite the potential advantages of a combination vaccine, there are also drawbacks. Negative interference may diminish the protective immune response to one or more of the components in a candidate vaccine, thereby prolonging the efforts needed for clinical development of the final vaccine. Combination vaccines are more prone to shortage due to their complex nature and the increased risk of a batch not passing one of the numerous tests in vaccine control. Combination vaccines may lead to shortages of the monovalent vaccines in the combinations; furthermore, monovalent vaccines may not be produced any longer due to limited demand. These consequences may cause problems in industrialized countries and in developing countries.

While any vaccine candidate must be judged against contemporary standards of safety, immunogenicity, and efficacy, some of the described vaccine associations from the literature might still become new combination vaccines. Beyond the enormous resources required, other crucial factors are likely to effect development, namely the perceived necessity of the combination, and its cost-effectiveness.[95–97]

In spite of such challenges, some of the vaccine associations explored in the past warrant reconsideration as targets for new combination vaccine development.

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Conflict of interest: All of the authors were employed by the Medical Affairs department of Aventis Pasteur during the preparation of this article. The authors do not expect to gain any financial benefit if any potential combination vaccine proposed in this paper were to be developed.

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