

Issues in selection of DTwP-based combination vaccines

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Abstract

This study examines regulatory, supply, acceptance and financing issues of combinations based on diphtheria–tetanus–pertussis (whole cell) vaccines (DTwP). These combination vaccines are currently produced in Europe mostly for export. Future regulatory oversight issues could have an impact on their availability. Before use of acellular pertussis-containing vaccines, the number of doses of DTWP vaccines offered in response to United Nations agency procurement tenders far exceeded the projected demand. Current demand and supply are converging. Most of that supply comes from developing country manufacturers, a potential new source of combination vaccines as well. The expected development and use of DTWP-based combination vaccines raises antigen allocation issues that could further affect supply. These combination vaccines have strong programmatic advantages, but pose complex selection issues involving disease burden, presentation, and availability of long-term financing. Vaccine price is not the major driving factor. A model examining important selection factors for regional country groupings provides predictions that have been validated by decisions on use of DTWP-based combination vaccines. This model may be useful in providing long-term uptake projections for other combination vaccines.

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1. Introduction

Combination vaccines, the best known of which is the traditional diphtheria–tetanus–(whole cell) pertussis (DTWP) vaccine, have been used for many years and offer several advantages, including a reduced number of injections, with a concomitant drop in syringe use and exposure to expipients, adjuvants and preservatives, and a non-disruptive way to introduce an additional antigen, such as hepatitis B (hep B) or *Haemophilus influenzae* type b (Hib) vaccines, into an immunization programme. Recent experience with DTWP-based combinations has attested to their enormous programmatic desirability. Despite their advantages, however, use of such combinations could limit programme flexibility and affect the supply of traditional vaccines. The purpose of this paper is to examine issues and implications surrounding the selection and use of DTWP-based combination vaccines. A summary of such vaccines currently available is given in Table 1.

The pros and cons of such combination vaccines are summarized in Table 2.

2. Issues raised in use of combination vaccines

2.1. Regulatory issues

There are several special considerations for regulation of combination vaccines compared to a new single component vaccine. These include the need to demonstrate the safety and efficacy of each component in the combination, which may be difficult if there are no serological coordinates of immunity [1]. Furthermore, the response to each antigen in the combination may be adversely affected by interference with other components.

A special issue is the availability of continued regulatory oversight for these DTWP vaccines that come under the central regulatory procedure of the European Medicines Evaluation Agency (EMA), e.g. those containing antigens based on recombinant proteins, such as hep B, and ultimately all new products manufactured in Europe. These products may be considered for licensing only if they have a market in Europe. Currently, most combination products marketed in Europe are based on acellular pertussis vaccine, and the trend is for even fewer European countries to use DTWP-based combined vaccines. Even those products already licensed by the EMA could have their marketing authorization withdrawn if they are not marketed in Europe for a specified period of time. This issue must be resolved to avoid a supply crisis.

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Table 1
Availability of DTwP-based combination vaccines

Specific combination	Status
DTwP–hep B	Produced by one manufacturer in Europe; under development by several developing country manufacturers
DTwP–Hib	Produced by two manufacturers in Europe and one developing country manufacturing group; US manufacturer has left market
DTwP–DTwP–Hib	Produced by one manufacturer in Europe; under development by several manufacturers in both industrialized and developing countries

Table 2
Pros and cons of DTwP-based combination vaccines

Pros	Cons
Fewer injections	Limited supply
Lower cumulative exposure to thiomersal	Higher prices, and higher impact of wastage
Large programmatic advantage for addition of desired antigen	Limited programmatic flexibility (i.e. need for birth dose of hep B)
Minimize “leakage” of vaccines that could be used for non-infant populations from the system	Impact on total DTwP supply
	Often available only in lower dose presentations, with impact on cold chain capacity

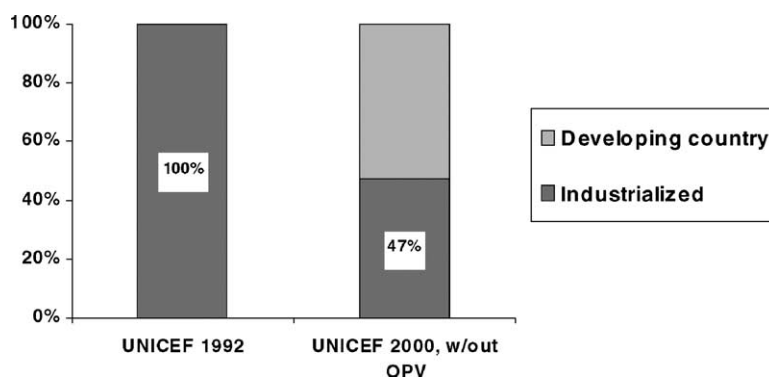


Fig. 1. UNICEF spend distribution for public sector vaccine purchases. Adapted from data supplied in Mercer Management Consulting study for GAVI Financing Task Force and Vaccine Fund 2002, Whitehead, personal communication, 2002.

2.2. Supply issues

Currently suppliers of DTwP vaccines for UN agency purchase [2] include two developing country manufacturers and three in industrialized countries. In practice, the vast majority of DTwP (77%) comes from one developing country manufacturer. The amount of DTwP offered in response to global tenders is just meeting global demand, a situation that has changed drastically since 1999, when offers exceeded demand by four-fold [3]. Part of the reason for this is the switch in production from whole cell to acellular pertussis components for DTP vaccines by several producers, linked to higher prices and higher profits for the acellular product.

Another reason is the general shift to developing country suppliers as a consequence of diverging vaccine markets. The source of traditional vaccines to UNICEF has shifted dramatically towards developing country suppliers since 1992. Fig. 1 shows this trend clearly. Thus, the DTwP supply appears to be shrinking, and the proportion from the industrialized world is almost minuscule.

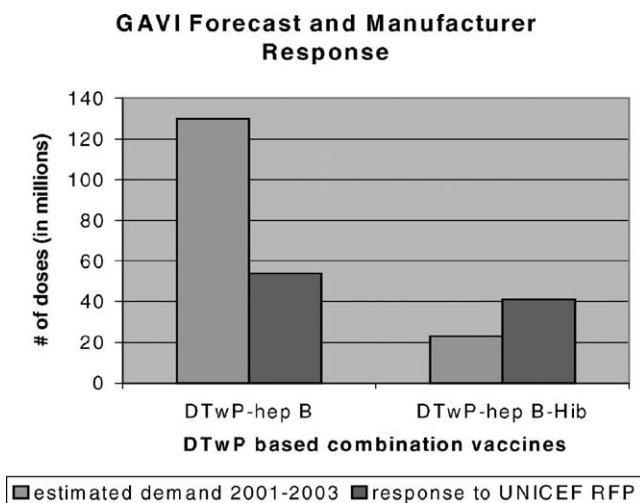


Fig. 2. GAVI forecasts and manufacturer responses to UNICEF tender. Sources: GAVI Financing Task Force Forecasting subgroup and UNICEF supply division.

This in turn impacts antigen allocation for combination vaccines. Currently, the only global source of DTwP–hep B combinations is Glaxo SmithKline Biologicals (GSK), which obtains whole cell pertussis component exclusively from other companies. This is a major factor limiting additional supply of this product (GSK personal

communication, 2002). Fig. 2 shows the resulting supply constraints: (1) a limiting amount of DTwP meant that the manufacturer allocated this scarce resource into DTwP–hep B–Hib, presumably because of higher profit margins and a secure market in the Americas, while (2) most countries initially eligible for funding support to

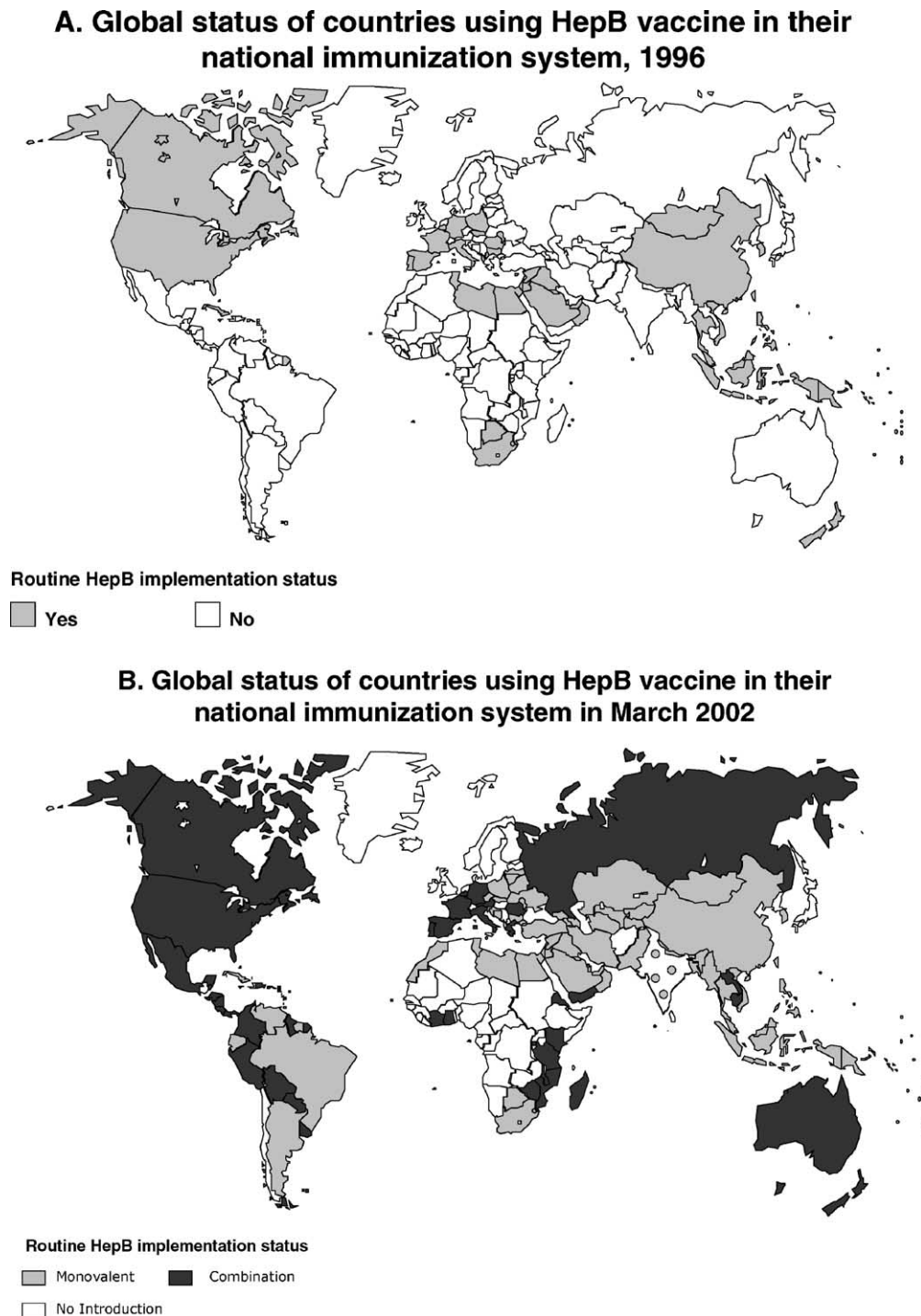


Fig. 3. Introduction of hepatitis B vaccine into immunization programmes: (A) in 1996; (B) in 2002, showing the increasing importance of combination vaccines in countries introducing this antigen. Source: country data reported to WHO.

A. Global status of countries using Hib vaccine in their national immunization system, 1997



Routine Hib implementation status

■ Yes □ No

B. Global status of countries using Hib vaccine in their national immunization system in March 2002



Routine Hib implementation status

■ Monovalent ■ Combination
□ No Introduction

Fig. 4. Introduction of Hib vaccine into immunization programmes: (A) in 1997; (B) in 2002, showing the impact of combination vaccines. Source: country data reported to WHO.

buy these combination vaccines through GAVI and the Vaccine Fund¹ opted for the simpler, all-liquid product,

¹ GAVI and the Vaccine Fund provide support for introduction of hep B- and Hib-containing vaccines to the poorest countries in the world. These countries can choose the antigen(s) they want to introduce, approval being based on a rigorous preparatory process in country and recommendations of an independent review committee regarding that process (see <http://www.vaccinealliance.org>).

DTwP–hep B. Because of the supply shortage, GAVI was forced to make some allocation decisions that cut overall uptake of combination products in the first year. Thus the mismatch in supply and demand meant that neither the manufacturer nor the recipient countries were fully satisfied.

It is expected that this situation will ease somewhat as more manufacturers develop combination vaccines. Already

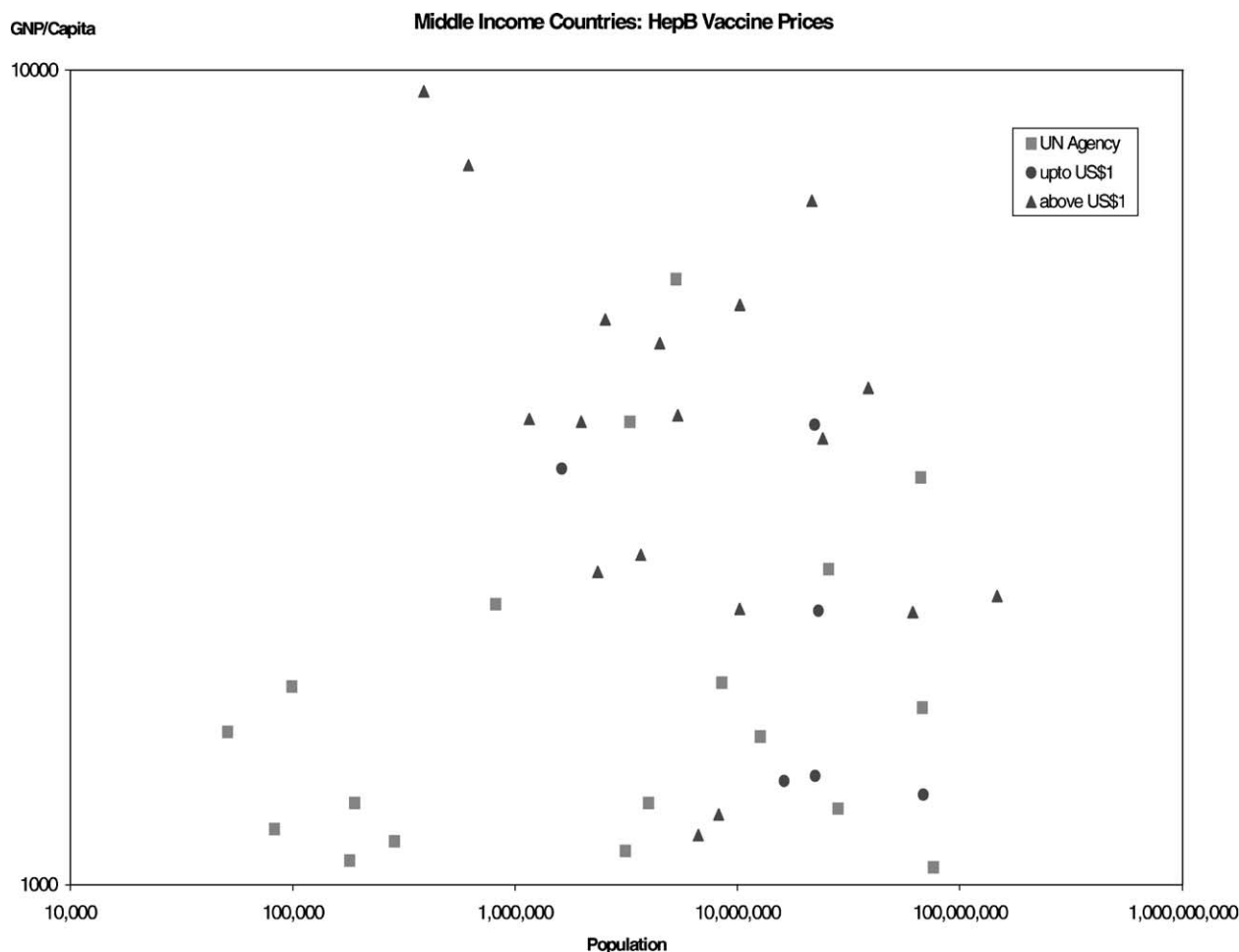


Fig. 5. Prices paid by middle income countries for hepatitis B vaccine as a function of GNP/capita. Source: country data reported to WHO.

developing countries are buying DTwP–Hib from two international manufacturers, and Brazil receives this product from local manufacturers. Projections are for additional supplies of DTwP–hep B vaccines in 2003 on some local markets and in 2004 internationally. This supply also depends strongly on developing country manufacturers. The Developing Country Vaccine Manufacturers Network, an alliance of manufacturers meeting or on track to international standards of quality, is a potential route to new supplies of these products.

2.3. Acceptance issues

Figs. 3 and 4 show, respectively the recent uptake of hep B and Hib vaccines in the developing world. It is clear that the availability of combination vaccines, the major formulations for supply of these antigens financed by the Vaccine Fund for the lowest income countries, has had considerable impact on their uptake. Most countries proposing to add hep B opted for DTwP–hep B vaccine. Virtually, every country receiving Hib vaccine through the Vaccine Fund has received DTwP–DTwP–Hib.

Despite the availability of combination vaccines and financing, uptake is not uniform throughout the world. There are several factors that influence vaccine selection: price, the proportion of vaccine expenditures as part of the overall health budget, pressure of immunization partners, including donors, and the perception of need, including the disease burden. In 2002, the Strategic Advisory Group of Experts (SAGE) to WHO's Department of Vaccines and Biologicals noted that studies have shown the Hib disease burden to

Table 3

Price categories of middle income countries using hep B and Hib vaccines 2002

Number of countries	Hep B	Hib
Total	52	52
Using vaccine	41	27
UN agency price	14	19
Procuring low price ^a	9	2
Procuring high price ^b	18	5

Source: country data reported to WHO.

^a Below US\$ 1 per dose for hep B; US\$ 2.5 per dose for Hib.

^b Above US\$ 1 per dose for hep B; US\$ 2.5 per dose for Hib.

Table 4
Market characteristics comparison

Market characteristics	Africa, poorest countries	Latin America	Asia	Eastern Europe
Financial condition	GNP/capita <US\$ 1000	Generally middle income	Low and middle income, some very large countries	Middle income
General programmatic condition	Variable, many weak	Strong	Variable but many strong	Variable but many strong
Programmatic flexibility	Limited flexibility	Possibility of flexibility	Possibility of flexibility	Historical lack of flexibility, but now flexible
Ability to make decision on vaccine utilization	Lack of national infrastructure and vaccine advisory committees, selection based on greatest perceived need	National advisory committees constituted in most countries	National autonomy in selection	Strong decision making power; use of combinations with IPV and acellular pertussis
Local vaccine production of antigens	None	Some, including development of combination vaccines	Strong, with many combination vaccines in development	Limited
Hib disease burden	High but many urgent priorities	High burden with several studies already performed	Low, few studies	Low to medium, few studies
Hep B disease burden	Very high	Lower (priority for Hib above hep B)	Very high, high priority, need for birth dose	Very high, high priority, need for birth dose
Prediction	High desire for DTwP–hep B; lower uptake of Hib-containing vaccines	High uptake of DTwP–Hib, and willingness to buy combos with inexpensive extras (like hep B)	Hib will be a low priority; hep B unlikely to be used in combined form	Low use of DTwP-based combinations

be lower in some countries, including Asia, and concluded: “SAGE reaffirms the WHO position recommending introduction of Hib vaccine as appropriate to national capacities and priorities. Most studies from mainland Asia indicate a relatively low incidence of Hib meningitis, data that are important for country-level prioritization. Additional Hib vaccine impact studies on the burden of pneumonia in Asia are needed to clarify the utility of the vaccine [4]”. These disease burden data likely explain the especially low uptake of Hib vaccine in Asia.

2.4. Financial issues

Despite the advantages of combination vaccines, their use can limit pricing flexibility. If a country decides to buy a DTwP–hep B combination vaccine, the product from the current sole source costs more than the two components. This is partly due to development and licensing costs of a new formulation. In addition, DTwP and hep B vaccines can be bought from other suppliers for a total of about US\$ 0.40 per dose in multi-dose presentations, while the combination product costs more than twice that amount. This higher price is at least partially offset by lowered syringe and delivery costs, however; the established programmatic advantages of the combination product are difficult to cost.

The issue of financial sustainability—the available of long-term financing for a product after the 5 year term of the Vaccine Fund support is over—is an important consideration for Vaccine Fund-eligible countries. This may have inhibited uptake of Hib-containing products, since a three-dose course of the pentavalent DTwP–Hib vaccine at US\$ 3.50 per dose, costs ten times more than the total expenditures for all the other vaccines in a typical national immunization programme.

For middle income countries however, price seems not to be an overriding factor. Fig. 5 shows that price is not the major predictor of uptake. Of 52 middle income countries (GNP per capita between US\$ 1000 and US\$ 10,000 per year), 41 are using hepatitis B vaccine. When hep B prices were divided into three categories: UN global price, less than US\$ 1 per dose (for procuring countries) and more than US\$ 1 per dose, the result was as seen in Fig. 5, where it is clear that vaccine price paid is not related to national wealth. Fourteen countries use the UN procurement system, 9 procuring countries are paying less than US\$ 1 per dose, and 18 are paying more than US\$ 1 per dose (See Table 3). Table 3 also summarizes similar information for Hib vaccine prices.

There are several considerations that go into the price: presentation (number of doses per vial), combinations, shipment and specification issues, and payment schedules. Countries that are paying higher prices may have selected single dose presentations and/or more sophisticated formulations. However, the inescapable conclusion from the information

in Table 3 and Fig. 5 is that price is not the major effector of uptake of hep B or even Hib vaccines for middle income countries, as many of the poorer countries are paying premium prices.

3. Predictions for uptake

The available data allow the generation of a model to predict uptake of combination vaccines. This is shown in Table 4, where market characteristics are tabulated for different regions of the world and antigen uptake in the form of combination vaccines is predicted. Based on the knowledge we have to date, most of these predictions are upheld, as can be seen in Figs. 3B and 4B. This type of analysis can serve as a basis for long-term projections for future combination vaccines.

4. Lessons for the public health community

The current analysis supports strongly the concept that price alone is not the major predictor of uptake, especially for combination vaccines. Countries will pay a premium for an additional antigen in a combination only if it adds value. The value added for a particular antigen will differ across countries and regions, depending on epidemiological and

other factors. The key is a real or perceived programmatic need, which can often offset vaccine price considerations. By adopting an approach more tailored to regional needs for long-term forecasting, the public sector may be able to develop more robust estimates of demand projections for the long-term.

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References

- [1] Goldenthal KL, Falk LA, Ball L, Geber A. Prelicensure evaluation of combination vaccines. *Clin Infect Dis* 2001;33(Suppl 4):S267–73.
- [2] http://www.who.int/vaccines-access/vaccines/Vaccine_Quality/UN_Prequalified/UN_Prequalified_producers.htm.
- [3] UNICEF 2001, Vaccine security: ensuring a sustained, uninterrupted supply of affordable vaccines. E/ICEF/2002/6, 21 December 2001.
- [4] World Health Organization, Vaccines and biologicals, Weekly Epidemiological Report. vol. 37. 13 September 2002.