

Divergence of vaccine product lines in industrialized and developing countries

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Executive Summary

This study examines the hypothesis that the suspected divergence of vaccine product lines between industrialized and developing countries could threaten the public sector vaccine supply goal to ensure availability of quality affordable vaccines to meet priority needs of developing countries. The available evidence suggests that there are two types of products. The reasons for this stem primarily from epidemiology and perceived relative risks. The study focuses on the latter situation, in which one product is substituted for another already existing product against the same disease, such as whole cell *versus* acellular pertussis or oral *versus* inactivated polio vaccine.

The characteristics of the public sector market are examined in terms of type and volume of products being requested. It is noted that developing country and emerging economy manufacturers are playing an increasing role in vaccine supply at the global level.

The implications of product divergence on supply, price and regulation of vaccines for the developing market are considered. Supply is becoming limited for several products, and there will be an increased competition for investment in new capacity from higher margin products. Production costs overall will continue to rise as regulatory requirements increase. Regulation of products produced by industrialized country manufacturers for developing country use will pose challenges, but these can be addressed. However, it will be important to avoid the perception that two types of products designed for two markets imply two levels of quality.

The study concludes that while product divergence may not be an ideal situation, it will continue for some products for at least the medium term. To meet the demand for developing market vaccines, it will be important to encourage both industrialized country and developing country/emerging economy manufacturers to stay in the market. WHO and its partners will need to send a strong message that this product line divergence is not a reflection of quality but a conscious choice to meet the needs of developing country immunization programmes in the optimal manner.

Background

The goal of vaccine supply efforts in the public sector is to ensure that high quality vaccines are developed in adequate capacity and supplied at reasonable prices to meet the priority needs of developing countries. Recently there has appeared a divergence in product lines between developed and developing countries. The aim of this study is to assess the extent of the divergence and its implications, both good and bad, and to better understand how the private and public sectors can work together to manage the situation.

Data for this study were obtained from UNICEF Supply Division,¹ and the Pan American Health Organization (PAHO) Revolving Fund,² from WHO files, from interviews with manufacturers and immunization officials, and from publicly available material such as websites.

The Market

Table 1 lists some of the products that are available and in use in the developing world compared to the industrialized world. Whole cell pertussis (wP) and oral polio vaccine (OPV) are overwhelmingly used in the developing world, while acellular pertussis (aP) products and inactivated polio vaccines (IPV) are more prevalent in the industrialized country market. There is a trend towards more and different antigens, different combination vaccines and different serotypes in the industrialized world. Finally, there are differences in product presentation, with multidose vials containing thiomersal as preservative common in the developing world. Some of the differences are based on epidemiology, real differences in disease burden (e.g. 7-valent pneumococcal vaccines, meningitis C conjugate) or the desire and ability to add new antigens (e.g. measles-mumps-rubella, hepatitis A). The differences in epidemiology are real, are further exemplified by vaccines against HIV/AIDS and malaria, and will need a concerted effort. They are not the main focus of this presentation.

The biggest change in product lines is rather based on the threat of adverse events. These differences include wP vaccines (phased out in Japan, North America, and most European countries in the 1990's), OPV (replaced by IPV in many industrialized countries when the threat of vaccine-associated paralytic polio overcame that of wild polio), mumps vaccines based on strains other than the Jeryl Lynn strain (replaced or discontinued in Japan, UK, US and Canada because of fears of vaccine-associated meningitis), and a trend towards phasing out of thiomersal (because of risks of mercury exposure in young children).

The developing country market is increasing, both in number of products being requested (Figure 1), and in volume (Figure 2) for additional antigens, although the demand in volume for traditional products (see demand curves in Figure 3), while fluctuating, is relatively stable.

A large portion of developing market demand is met through large procurement agencies such as UNICEF Supply Division and the PAHO Revolving Fund. A look at their mix of suppliers (Table 2) indicates an increasing proportion of suppliers from developing countries and emerging economies (DC/EE).

¹ We thank Mr Steven Jarrett, Deputy Director, and Ms Shanelle Hall, Contract Officer, UNICEF Supply Division, for their assistance in providing these data.

² We thank Drs José Luis Di Fabio and Otavio Oliva, RDV, SVI, WHO Regional Office for the Americas for their assistance in providing access to this information.

Table 1. Tailored products: serving different markets

Baseline	Tailored to the DC Market	Tailored to the Industrial Market
Measles	Measles	MMR
DTP	DTwP	DTaP
OPV	OPV	IPV
TT	TT (Td in some areas)	Td
Hep B	Monovalent DTwP-Hep B	Monovalent DTaP-Hep B DTaP-HepB-IPV-Hib Hep B-Hib Hep A-Hep B
Hib	Monovalent DTwP-Hib DTwP-Hep B-Hib	Monovalent DTaP-Hep B-IPV-Hib Hep B-Hib
Meningitis A/C polysaccharide	Meningitis A/C conjugate (wanted)	Meningitis C conjugate (Meningitis B/C conjugate)
Pneumococcal polysaccharide	11-valent conjugate (wanted)	7-valent conjugate 11-valent conjugate (under development)
Product presentations	Multidose Thiomersal	Single dose No thiomersal

Number of Products Requested, UNICEF and PAHO

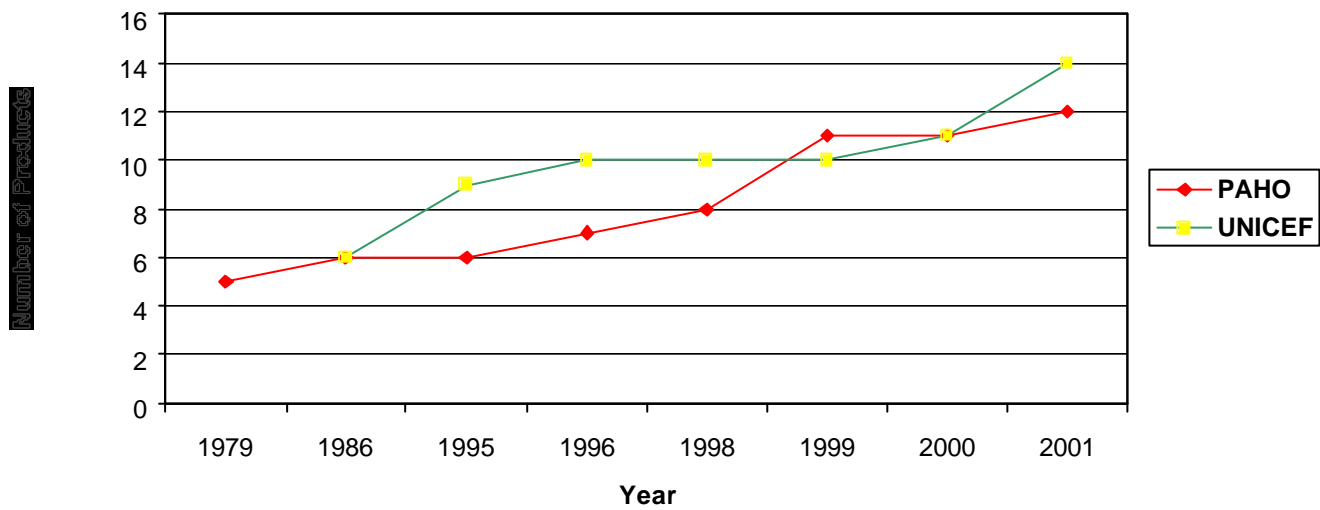
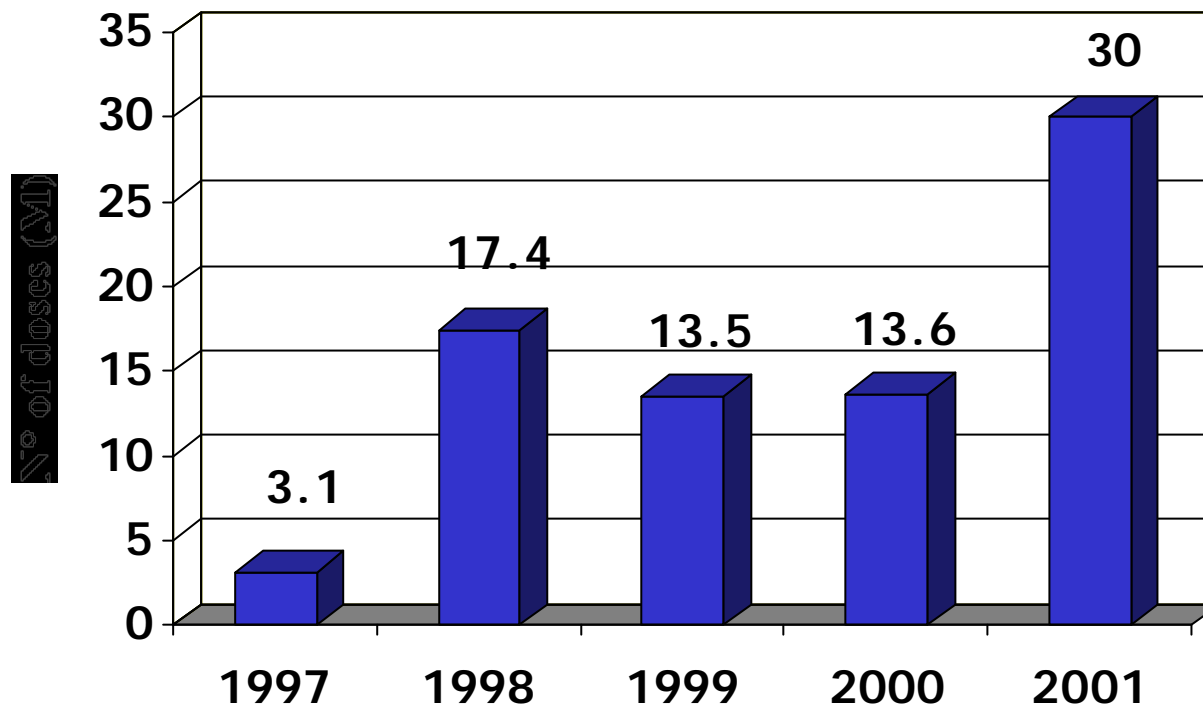


Figure 1. PAHO and UNICEF have increased the number of antigens demanded (Source: UNICEF SD and PAHO RF)



**Figure 2. For newer vaccines, demand is increasing (Source: PAHO RF).
PAHO demand for MMR, 1997-2001**

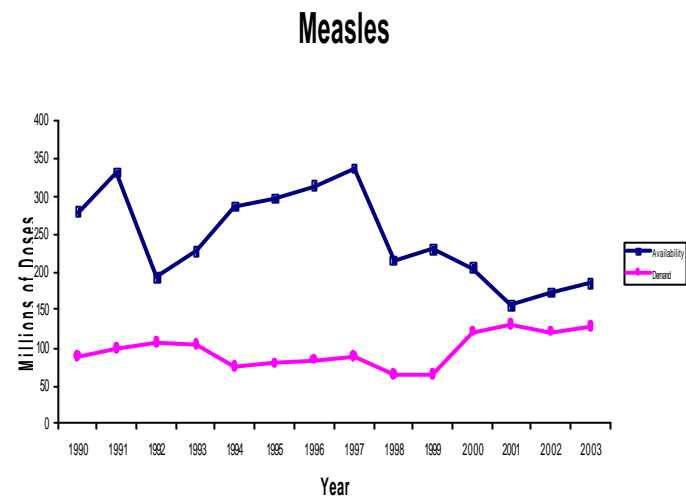
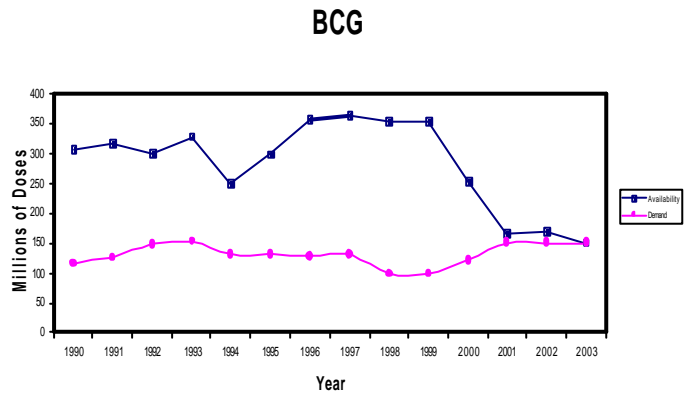
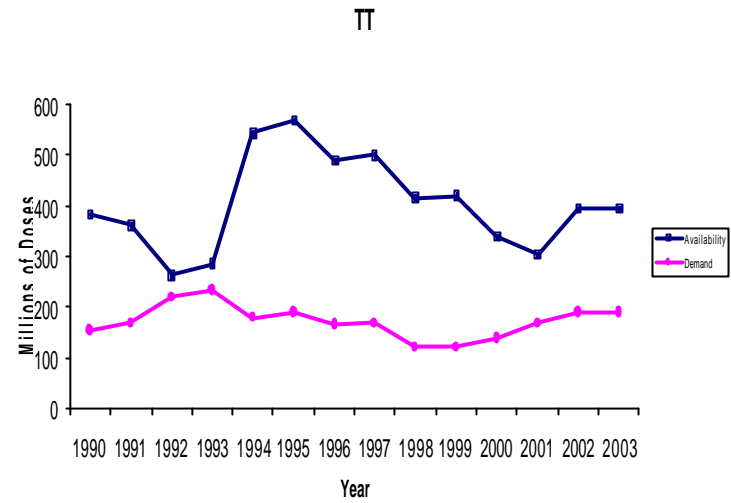
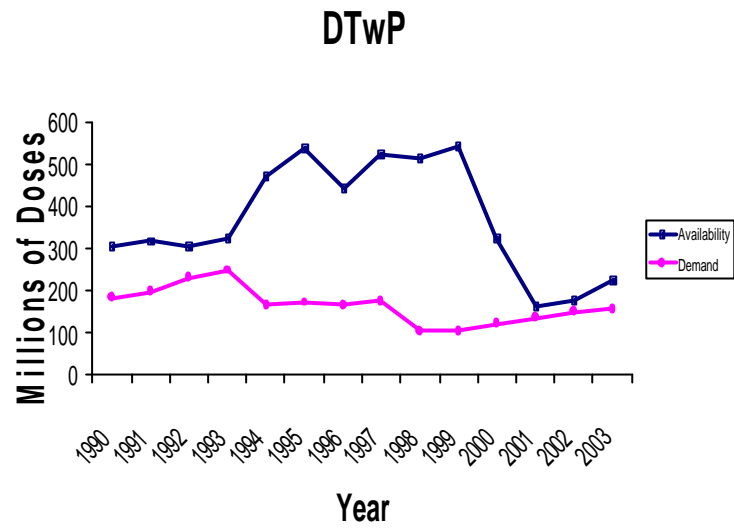


Figure 3. UNICEF demand and availability, 1990-2003 (Source: UNICEF SD)

Table 2. UN agency mix of suppliers – DC/EE manufacturers are shaded (Source: PAHO RF, WHO)

Vaccine	1986	1996	2001
Measles	Institut Mérieux SKB Sclavo Evans Connaught	PMC Biocine Il Zagreb SKB Biken Evans Serum India	Aventis Biken Serum India
Polio	Institut Mérieux SKB Sclavo Connaught	PMC Biocine SKB Chiron Behring	Aventis Chiron Vaccines GSK Biofarma
DTP	Institut Mérieux Connaught Swiss Serum Behring	PMC Serum India Swiss Serum CSL Biocine Chiron Behring	Aventis Biofarma CSL Serum India
TT	Institut Mérieux Connaught Swiss Serum Behring	PMC Human Serum India Swiss Serum CSL Biocine	Serum India Biofarma CSL Human
Hep B	--	SKB Cheil LG Green Cross	LG Green Cross Cheil (recomb)* Bharat* Shantha*
Hib combos	--	--	

These DC/EE manufacturers, as shown in Table 3, appear for the most part to be bypassing the products that are specifically tailored to the industrialized market (such as DTaP, IPV), and to be developing products that are again primarily tailored to the developing market.

Table 3. Product tailoring by manufacturers

Planned product
Current product

	Tailored to the DC Market			Tailored to the Industrial Market				New		Future	
	Measles	DTwP	OPV	MMR	DTaP	IPV	Mening C conjugate	DTwP-Hep B or Hib	Pneumo	Rotavirus	Multivalent meningitis conjugates
DC Mfgs											
<i>BioFarma</i>											
<i>Vacsera</i>											
<i>Razi/Pasteur</i>											
<i>Butantan/Biomanguinhos</i>											
<i>India Private Sector</i>											
<i>Cuba</i>											
<i>China</i>											
Industrialized Mfgs											
<i>Aventis</i>											
<i>Chiron</i>											
<i>CSL</i>											
<i>GSK</i>											
<i>Merck</i>											
<i>Wyeth-Lederle</i>											

Implications

We have next tried to analyze the implications of the current situation on three different areas: supply, price, and regulatory oversight. As Figure 3 shows, the availability of traditional products to the UNICEF market is converging toward demand, in contrast to the trend in recent years, when there was a large excess available to the UNICEF market. A large part of the availability for these vaccines (note that OPV is not included), about 65%, is being met by DC/EE manufacturers. Industrialized country manufacturers state that their capacity is over-saturated. It is expected that new investments in capacity will be made in the area of higher margin products. Already the developing market is seeing shortages of some products specifically targeted at their markets (e.g. yellow fever and meningitis A/C polysaccharide vaccines) because capacity is saturated, and, in some cases, as a result of competition for available capacity from higher margin products. Sudden changes in demand or supply (e.g. manufacturing failure of one suppliers) may threaten public sector immunization programmes. However, moving towards a single product line across the globe would not necessarily relieve these shortages. Available capacity, for example, of aP is to date extremely limited.³

³ It is important to note that these products have not been recommended for use in the developing country market, based on epidemiological and economic considerations. This may explain in part the limited supply.

At the same time, prices are going up. A need for new investment in capacity, coupled with higher regulatory costs overall, has caused this. The relative stability of prices for some traditional vaccines (Figure 4)⁴, can be attributed to the large proportion provided by DC/EE manufacturers. As they in turn meet capacity and regulatory constraints, it is expected that the prices of these products will rise as well. Prices for newer vaccines are orders of magnitude larger than prices for the traditional vaccines (Figure 5). Thus we can expect prices for all vaccines to increase.

Regulatory issues comprise a barrier to the traditional picture of cheap developing market vaccines as they impact both prices and capacity. Regulatory requirements are increasing, partly because the decreases in vaccine-preventable diseases have left the public sector more vulnerable to perceived risk. This trend, which has accounted for much of the product line shift in the industrialized world, will be replicated in the developing world as disease incidence falls. This will require an increased effort by the public sector to ensure one standard of compliance across products, and increased advocacy for cost-effectiveness of vaccines.

Moreover, the diverging products may pose regulatory barriers as the national regulatory authorities of the country of manufacture may be unwilling or unable to provide a marketing authorization for these products. Already the European Union has advised that combination vaccines built on DTwP going through the European central licensing procedure (e.g. DTwP-Hep B) may not be marketed within the EU. This poses an issue for their future regulation. Options are being explored and the situation seems soluble; nevertheless, product divergence does raise an issue in terms of regulatory oversight.

Discussions with the United States Food and Drug Administration in addition have indicated that regulation of products produced in the United States exclusively for the developing market would need to be done outside of the United States. This accentuates the need for strong regulatory authorities in at least key developing countries, and strong epidemiological expertise to guide decisions on product use. Finally, as DC/EE manufacturers become even more of a factor in supply to the developing market, their national regulatory authorities will need to demonstrate their ability to provide competent and credible regulatory oversight.

⁴ OPV, not shown, has had increases in price. The demand and supply of OPV is a special situation because of the acceleration of the polio eradication initiative.

UNICEF Average Prices 1990-2003
TT, DTWP, BCG, Measles

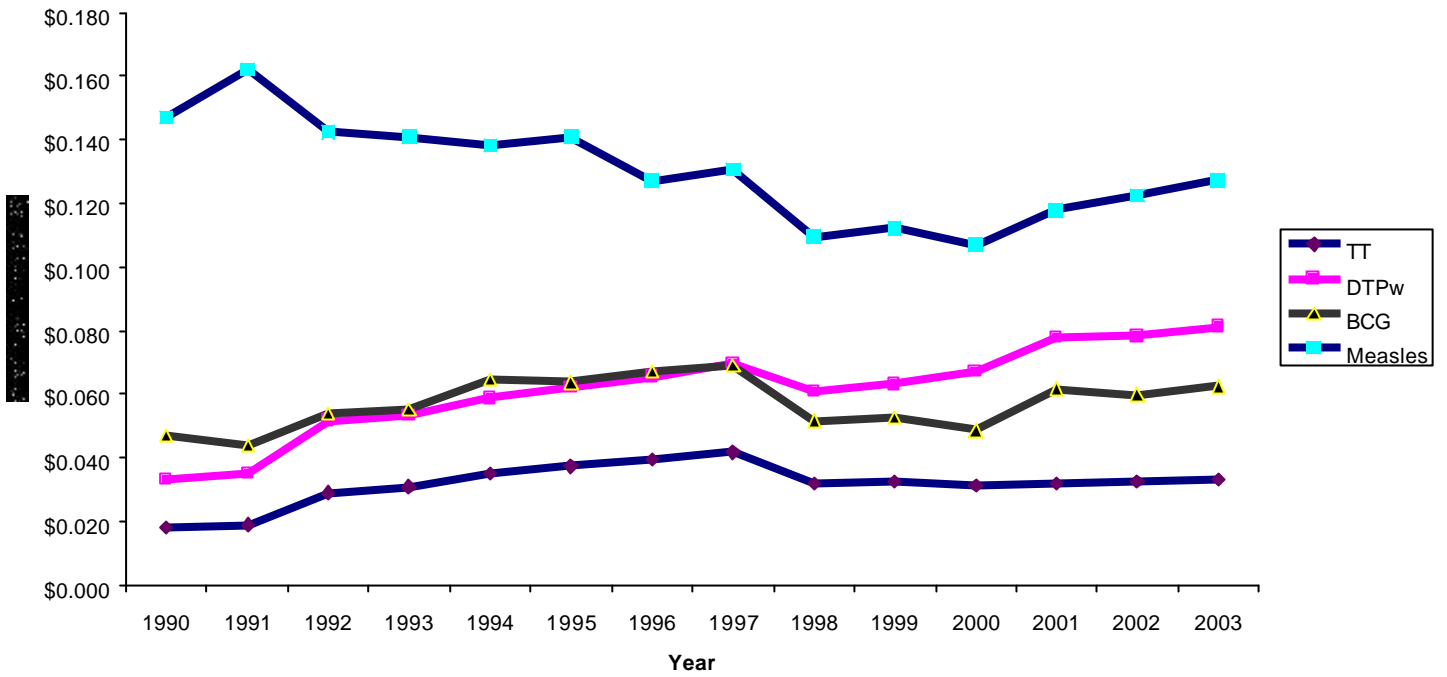


Figure 4. UNICEF average prices (Source: UNICEF SD)

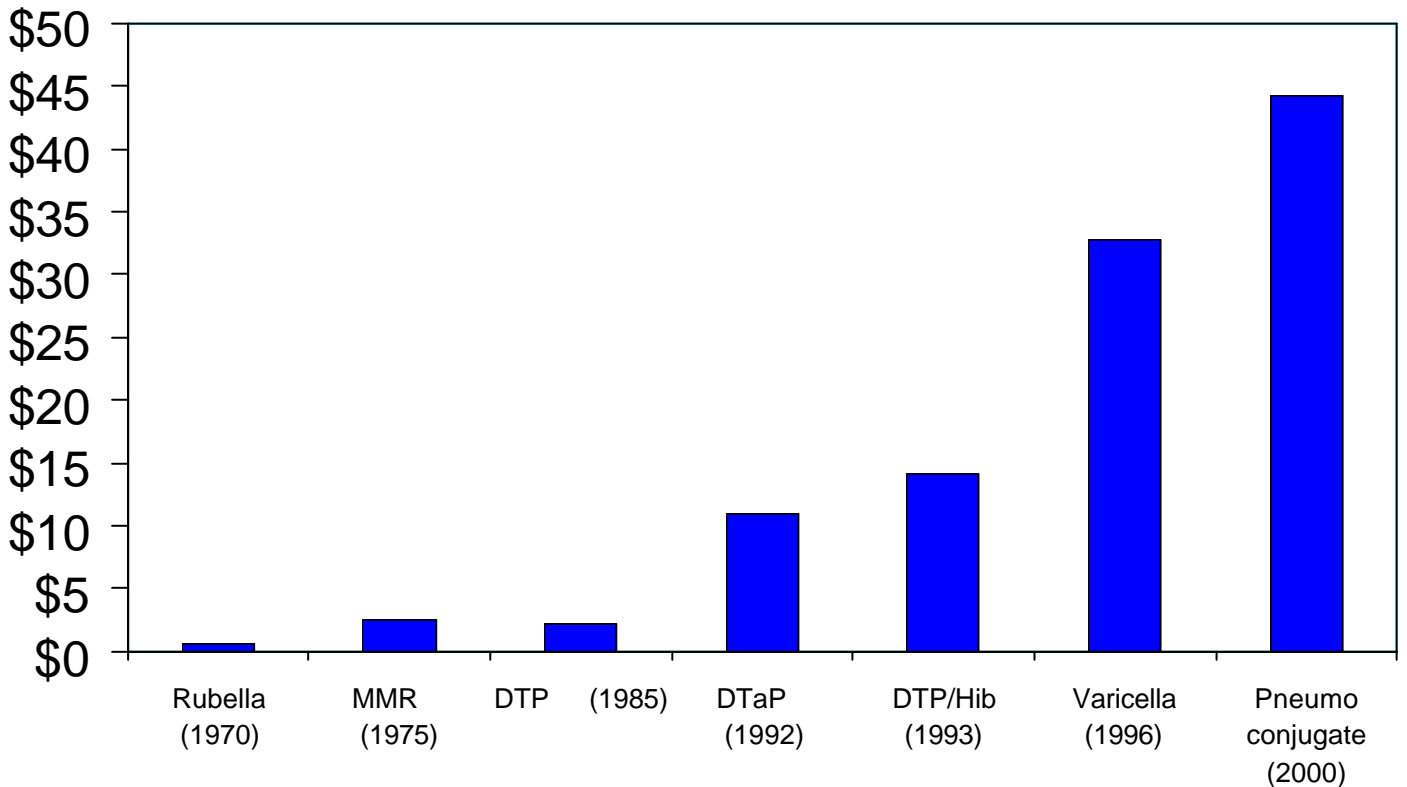


Figure 5. Pricing of traditional vs newer vaccines (Source: CDC contract prices, 1970-2000)

Conclusions

The issue of diverging product lines is a real one. Even though this situation is not ideal, it is necessary. Some of the divergence is based on different epidemiological needs and will be with us as long as there are two worlds. Other differences in cases where the industrialized country market has phased out products due to real or perceived risks (e.g. wP) will remain for at least the medium term, owing to considerations of vaccine delivery strategies, pricing, and supply.

Production costs are going up, capacity may be saturated, and regulatory needs are increasing, so it is important to have a spread of manufacturers in the market to attenuate some of these changes.

Regulation of products specifically tailored to the developing market may pose problems, but they appear to be surmountable. In any case, there will be a need to strengthen national regulatory authorities in key developing countries including those where manufacturing is in place for the global market, and to increase the epidemiological capacity to guide decisions on vaccine use.

Recommendations

The evidence to date suggests that there are instances of diverging vaccine product lines in industrialized and developing countries. While necessary in some instances based on epidemiologic and feasibility considerations, this situation could lead to difficulties of supply, higher prices, and barriers to vaccine registration and regulatory oversight. To manage this divergence and still meet the goal of ensuring that high quality vaccines are developed in adequate capacity and supplied at reasonable prices to meet the priority needs of developing countries, SAGE advises WHO and its partners to:

- Develop strong positions on product selection and communicate the reasons for these positions to minimize issues related to perceived safety and quality of developing market products;
- Keep key manufacturers in the market through ensuring that incentives, such as solid forecasting and stable purchasing, exist for manufacturers to assure the supply of needed products;
- Ensure adequate and appropriate systems exist for licensing and regulatory oversight to assure quality, safety, and efficacy of these products.