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Development of Vaccines to Meet Public Health Needs: Incentives and Obstacles

Phillip K. Russell*

Introduction: Children's Vaccine Initiative

Experiences with the Children's Vaccine Initiative (CVI) are the source of many ideas and things I address here. It was an organized attempt by the international public health community to bring new technology and a new generation of vaccines into global use. The initiative was led by the Rockefeller Foundation, and included the World Health Organization (WHO), the National Vaccine Program (NVP) and UNICEF. The CVI was initiated because of the tremendous promise the biotechnology revolution offered in terms of new vaccines and new ways of immunizing the world. The global preventive medicine and public health effort is still struggling to control infectious diseases on a global basis. It has accomplished some wonderful things — irradiation of smallpox, partial irradiation of polio (we'll finish that off by the end of the century, I hope) — but still many millions of children die every year from preventable diseases.

Part of the problem is the difficulty of delivery of vaccines and vaccines that have a host of deficiencies from the point of view of public health. The CVI sought to improve the efficiency of vaccination around the world by (1) building new vaccines that could be given in fewer doses, (2) immunizing in one or two doses rather than three or four, (3) including as many antigens as possible into a single combination vaccine to reduce the burden on the logistical system, (4) expanding the coverage to include new vaccines that are currently not available on a global basis, (5) lowering the reactogenicity so that the vaccines are more acceptable to mothers, children and physicians, (6) giving them orally, if possible, to lower costs and the dangers and burdens of

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needles and syringes, and (7) improving their heat stability. Heat stability is an incredibly important asset in the tropical world; refrigeration needed to get vaccines into villages in the far reaches of Africa and India has a huge cost. Of course, the bottom line is that the public health community doesn't have a lot of money. So affordable access is an important goal.

These are CVI targets, and there has been a global effort to work towards them over the past five years. Some progress has been made, but the combined issues of intellectual property, economics, and sociology put many obstacles in the way.

It's not just a global issue. The U.S. has its own difficulties in effectively immunizing its children. Hepatitis B is still not being universally used, and inactivated polio needs to replace the current oral polio. Measles still occurs throughout the nation, and as much as 50% of the population is underimmunized in some inner cities, for example, because of a fairly cumbersome vaccine schedule. The medical community would like to see one or two oral combination vaccines to take care of all vaccine-preventable diseases. Figure 1, below, shows the incredibly complex 1995 recommended immunization schedule from the Centers for Disease Control (CDC) — not only complex from the point of view of the schedule, but omitted explanations of choices go on for pages!

That schedule is a tremendous burden on the system¹ that has to deliver vaccines to children. This is an expensive schedule to deliver, and buried in it are vaccines like DTP that are 1950's technology. Why are we still using 1950's technology? Why do we not have combination vaccines we need and should have? Why haven't we been able to use the tremendous power and potential of the biotechnology industry and industrial research to produce new vaccines? The answers are complex — partly economic, partly regulatory, partly societal and, in this country, partly governmental incompetence. This complex situation is going to get much worse before it gets better.

We now have some combined vaccines (DTP and MMR), new pertussis vaccines being worked on by the National Institutes of Health

¹ Also, in the U.S. the system itself is also incredibly complex. It involves state and city health departments, public health clinics, private practice, HMOs and a whole spectrum between. And, it's changing as we speak.

(NIH) are expected within the next year or two. New pneumococcal vaccines are in the pipeline, a chicken pox vaccine has just been licensed and hepatitis A is to be added to the schedule. We're going to take an already cumbersome schedule and add more individual vaccines, and it will inevitably result in a detriment to the public's ability to be immunized.

Figure 1. Recommended Childhood Immunization Schedule — U.S. 1995[†]

Vaccine	Birth	2 Mos.	4 Mos.	6 Mos.	12 Mos.	15 Mos.	18 Mos.	4-6 Yrs.	11-12 Yrs.	14-16 Yrs.
Hepatitis B	HB-1	HB-2	HB-3							
Diphtheria-Tetanus-Pertussis (DTP)		DTP	DTP	DTP	DTP or DTaP at ≥15 months			DTP or DTaP		Td
<i>Haemophilus influenzae</i> type b		Hib	Hib	Hib	Hib					
Oral Poliovirus		OPV	OPV	OPV	OPV			OPV		
Measles-Mumps-Rubella (MMR)					MMR			MMR* or MMR*		

DTP: Includes acellular pertussis.
[†] Recommended vaccines are listed under the routinely recommended ages. Bars indicate range of acceptable ages for vaccination. Adapted from MMRW (weekly), Jan. 1995. Source: Advisory Committee on Immunization Practices, American Academy of Pediatrics, and American Academy of Family Physicians.
 * The second dose of MMR vaccine should be administered *either* at 4-6 years of age *or* at 11-12 years of age.

International Vaccine Industry

To understand the problems involved in putting technology to practical use, one thing to look at is the industry that produces these vaccines. We rely on the industry for industrial development, instrument development and production, as well as for quality control. In the international world, it's about a \$3 billion a year industry. It is dominated by large multinational corporations, such as Merck, Pasteur-Merieux-Connaught, Biocine-Sclavo, Smith-Kline-Beecham and Wyeth-Lederle. Many are part of the global programs for vaccination. Some U.S. companies, for example Merck, have a different international status than the others because they don't sell vaccines to UNICEF. The U.S. vaccine industry is separate from European-based multinationals because of U.S. regulatory and other factors.

Many vaccines are made by big public-sector manufacturers. For example, Brazil, China, Indonesia and Vietnam largely produce their own DTP. Yet, they are capable of making only commodity vaccines using older technologies unencumbered by intellectual property. They have no capability for developing new products and will depend on technology transfers from either large multinationals or smaller public-sector manufacturers. There's a couple of interesting very small public-sector manufacturers in this country: Michigan Department of Health and Massachusetts Department of Health, as well as other state manufacturers and distributors of vaccines. Some smaller countries, such as Thailand and the Philippines, have small public-sector manufacturers. And of course, the biotechnology companies are playing a bigger and bigger role in the international vaccine industry. It's a very complex industry, and it is a tremendous challenge to bring it up to the level needed to produce the next generation of vaccines — for southern as well as northern countries.

Industry and Market Structures Affecting Vaccine Prices

The vaccine market is also complex. Only in the last couple of years have studies shed some light on how it really works. One aspect of it is multiple tiers of prices. Large corporate multinational manufacturers have at least four price levels. They sell at the private retail price throughout the world wherever they can get licenses for their products.²

They negotiate prices with their own governments, usually at lower than private sales prices but still high. They also negotiate prices with underdeveloped countries that buy vaccines. The bottom tier is very large volume sales to UNICEF or Pan-American Health Organization (PAHO). These prices are probably at marginal production costs with fully amortized facilities and no royalties. These sales produce only a modicum of profit, but they are nonetheless important for some manufacturers. Obviously these are commodity vaccines, selling at approximately eight cents a dose for polio and ten cents for DTP.

The U.S. domestic market has three tiers. It is protected from the rest of the world partly by our regulatory system but partly by established buyer practices. Of course, U.S. manufacturers sell at retail, the highest prices, with lower negotiated prices for the large health care organizations. The third pricing tier is the government contract price, which has become incredibly contentious in the last two years or so with respect to the Vaccines for Children program. Because children's vaccines in the U.S. are no less than 50% of the total vaccine production and may be as high as 75–80%, this is a very important aspect of the market dynamic that I discuss in more detail later. It has had a tremendous impact on the way the vaccine industry invests in new technology and research.

The vaccine industry is changing dramatically. Vaccine technology is changing, creating a push from the bottom up to produce new products. The companies are working rapidly with new combinations where they can. The use of new adjuvants is a very promising set of technologies. There is tremendous competition at the technical level and also tremendous competition at the manufacturing level. Technologic changes and market changes are driving the companies into larger and larger aggregates, and there are predictions of maybe one or two monstrously large vaccine companies in the future. Consider that Pasteur-Merieux, Lederle and Merck have marketing agreements with respect to Europe, and that includes Commonwealth Serologic Laboratory of Canada. Other companies that don't have big marketing organizations do have other kinds of relationships, like Smith-Kline-Beecham with MedAmerica and Michigan State Health Lab.

² One interesting thing is that the private sales market in India is probably the largest in the world.

Biotechnology firms are vigorously working to produce new approaches and are forging impressive new alliances with big companies. They are driven by technology to share technologies that will produce better combinations, and they are also driven by marketing considerations. We're seeing a jump in cost from the commodity vaccines to the new vaccines which are heavily layered with intellectual property rights. I think the Hepatitis B vaccine manufactured by Merck and Smith-Kline-Beecham probably has about 30 associated patents. As we get into more and more complex combinations, the intellectual property situation gets much more complex.

The innovations brought about by these changes are very difficult to transfer to the developing countries; technology transfer is almost a dirty word in the international health business because of the difficulties in transferring the technology from either the public or private sector to developing countries. But because of the cost of vaccines and because of the nationalistic views of many countries in the underdeveloped world, the reliance on developing country manufacturing is increasing greatly and so the world supply of vaccines depends to a very large extent on manufacturing in developing countries. The international issues of the management of intellectual property rights and technology transfer are therefore becoming of ever greater importance.

Vaccine Development and Testing — U.S. Decision-Making

I'd like to turn now to how the U.S. develops, tests and brings vaccines into use, and to analyze the players and what they do, and how they contribute to either the progress or the chaos, depending on your perspective.

At the beginning of development in this country, we depend largely on the federal government, and to a lesser extent on the private sector, for basic research. The people who drive that are the individual investigators, the study sections at the NIH, the reviewers of the grants and NIH program managers. In the vaccine field, the direction of the research is driven by the quality of the science and the NIH is driven to some extent by the disease burden, with medical practitioners taking a look at this every five years to help it shape its program. That's almost entirely public-sector support at the basic research level.

Table 1
Decision-Making in Vaccine Research, Development, Purchase and Use

<i>Stage of RDA</i>	<i>Major Decision Makers</i>	<i>Basis for Decisions</i>
Basic Research	Investigators Study sections Grant reviewers NIH program managers	Scientific interest Quality of science Disease burden
Applied Research	NIH program managers Company R&D managers	Feasibility Disease priorities Commercial potential Patent position
Product Development	Corporate management	Feasibility Patent positions Market analysis Commercial potential Investment needed
Licensing	FDA	Safety data Efficacy data
Utilization	ACIP Redbook Committee	Disease burden Efficacy Effectiveness
Purchase	CDCP States Private buyers	Congressional action Program needs Price Recommendations of advisory committees

When you get into applied research, to develop a new product, you shift to a mixture of NIH program managers and the commercial sector, the latter coming in with corporate R&D and biotechnology. At that point, the responsibility for bringing products out of the research laboratory and into pilot production and testing shifts from the public to the private sector. Product development is fundamentally a corporate enterprise in this country. Although the NIH claims to be developing various vaccines, the fact is that all of the energy and direction is at the corporate level. The decision-making is driven by the probability of success, the feasibility of the project, the patent position and market analysis — standard commercial considerations that drive any industry. The user doesn't get any say about what is developed.

There is no organized structural input into the vaccine industry from folks who have to use them. Nobody asks those folks.

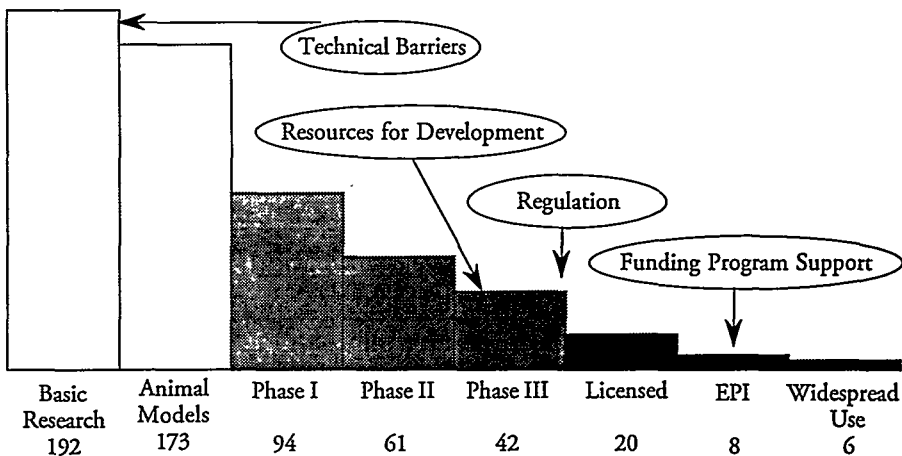
At the next level of development, responsibility shifts to the Food and Drug Administration (FDA) to approve the safety and efficacy data which is produced by the manufacturers. Interestingly, however, the content of licensing applications, schedules, and so forth are controlled by corporations. As licenses are negotiated and discussed, and until they are finally approved by the FDA, they are confidential. The rest of the world is shut out. The public sector cannot see what's going on between the FDA and industry. The FDA has the legal authority to determine what's on the package insert and the public recommendations.

Then, committees that deal with vaccine utilization, another government agency, give the FDA recommendations based on the scientific data and their views of the importance of the disease and the vaccine's efficacy. These are the Advisory Committee on Immunization Practices (ACIP), the Redbook Committee, and the Committee on Infectious Diseases of the American Panel of Pediatrics — a professional committee that has traditionally made vaccine recommendations. They may not agree with the FDA, but they have no effective way of altering the FDA's decision.

Purchasing decisions shift to another community basically related to public health. The CDC negotiates the federal contract every two years for vaccines, based on congressional action which may or not be rational and which may or may not have any relationship, in fact, to what public's health needs. The states have to look at the federal health initiatives, and of course, private buyers must deal with having the options of only what package other groups have recommended and the FDA has approved. There's no centralized way of influencing or planning this, to say nothing of directing it. It's a matter of great concern to many of us in the vaccine business who come at it from a public health perspective. For decades, every attempt to systematize this disjointed system, to bring together into some coherent national effort the people who bear the responsibility and who have decision-making authority, has failed.

As a result, one of the things we see is a difference between what's in the vaccine development pipeline and what comes out. Figure 2 shows vaccine development data from the NIH. There's a lot of vaccines in the basic research stage. Many even get into some sort of Phase I trials after they get over the scientific and technical barriers. Then, we get into Phase II and III clinical trials where the availability of resources for development becomes very dominant. Perhaps the most important consideration here is the willingness of the private sector to invest in product development. When private-sector investment has failed, it all adds up to very few vaccines. We need a coordinated push from beginning to end. Unless there is vigorous investment from the private sector, vaccines won't get through the pipeline. That's why we're so slow in developing the HIV vaccines, that's why we don't have a malaria vaccine, and that's why many of the vaccines that are beginning to come out took so long.

Figure 2
Obstacles to Vaccine Development[†]



Why did it take so many years to make the improved pertussis vaccine? There wasn't enough investment in that, partly because of the regulatory hurdles for vaccines, with the high levels of safety that have to be met and proven, and the very high levels of efficacy that have to be met and proven. The current numbers are maybe between \$150 -

[†] Source: U.S. Government Jordan Report 1994 — does not include HIV vaccine research, and basic research and animal models are not comprehensive given difficulty of defining and estimating number of research activities in these early stages.

\$200 million per product for R&D and clinical trial review. I think those are pretty good estimates. Getting on to vaccine licensing and distribution and use, there may be a public-sector financing or a social problem. Although this is not necessarily an U.S. problem, it certainly is a huge problem in developing countries, especially since new vaccines come with a much higher price tag than the previous ones.

What are the major obstacles to vaccine development? Market uncertainties are very high on the list, especially for those vaccines that will be largely used in public-sector programs. Children's vaccines are the worst, because there is no authority, no plan, that guides the industrial investor in which product to develop. The market uncertainties are exemplified by a tremendous controversy going on right now in the vaccine industry.

ACIP is considering a shift from the current oral polio vaccine to the inactivated product. The current oral vaccine has an estimated risk of one case of paralytic disease per 1 to 2 million individuals vaccinated, resulting in an average of about eight cases a year in the U.S. That cost was assumed to be justified because of the risk of importation of polio in the past. However, currently that risk is dropping because of global irradiation programs. Therefore the burden of those eight cases is being viewed as unnecessary and untenable, and a matter we ought to do something about. The problem is that we have to continue with some use of the oral vaccine to protect the population. There was insufficient forward planning to develop the intellectual basis on which to move ahead in a rational manner. The ACIP is threatening to make a recommendation that is not going to be approved by the FDA.

Manufacturers were not told (or asked) a couple of years ago to begin studies to get the necessary data for approval. The situation is the result of a breakdown of our advisory system and our planning system. It's a fascinating controversy because it contains the history of the rivalry between Dr. Jonas Salk and Dr. Sabin, and the ethical dilemmas of the risk to the individual versus the risk to the population and the rights of the individual versus the public health. It also raises other questions. Who's in charge of the Federal policy — the FDA or the CDC? Who's going to win a \$100 million — Lederle or Pasteur-Merieux? And who's got the most muscle in the distribution market?

It's a raging argument because it extends to many segments of our population. The industrial folks are going at it, and the academic people and pediatricians are squaring off against the public health people. This illustrates that market uncertainty may cause failure to bring the right products through, and it is related to poor government planning and coordination.

Government pricing policy poses another obstacle to vaccine development. In 1993, the fall-out from health care reform was the Vaccines for Children program that made children's vaccines an entitlement. Because of the way this program was structured, it would raise the level of federal purchases, at negotiated and legally capped prices, from 50–80% of the market. This caused immediate dismay in the vaccine industry, multinationals and biotech companies alike, and a marked diminution of investment in vaccine research. In a study, Mercer Management estimated that, in large corporations alone, the detriment to vaccine R&D was \$200 million a year, and all from one decision by Congress. That probably will be fixed this year, but nobody's quite sure how.

A further obstacle is the high cost of development. This cost is high because it includes the cost of failures as well as successes, and there is a high risk of failure. Lack of access to technology is also a critical obstacle to vaccine development, and therein lies one of our biggest problems. If I were to design a children's vaccine out of existing components, I would probably buy the tetanus from one company, the diphtheria from another, the acellular pertussis components from another, the hepatitis B from another and the adjuvant from somebody else. If you want optimal vaccines, you've got to aggregate the material from all over the place. We don't have the system to do it.

The technology we'd like to aggregate for investment in combination vaccines is spread among a host of corporations that don't get together on their own to produce the most optimal combination. They make deals they can make and know how to make, for their own reasons. So we're basically stuck with what individual companies come up with. There is communication between the public sector and the private sector, between the government agencies involved and the corporate R&D community, but it's very strained. It's very

contentious, and it's gotten much worse in the last few years. One of the things the Disabled Foundation is attempting to do is to develop a forum for effective communication between the vaccine users, nutritionists, practitioners, NIH program managers, states and cities, medical schools, public health systems and advisory groups. That is an incredibly difficult thing to do, and we do not currently do it very well.

Landmark Legislation Affecting Vaccine Development

I'd like to comment on two very important pieces of legislation that have influenced the vaccine field dramatically. Public law 99-660 is a visionary law that set in place the National Vaccine Injury Compensation Program, which did a tremendous amount to save the U.S. vaccine industry because it put in place a rational scheme for compensation for vaccine injury, a system I think is working very well from everything I've heard and everybody I've talked to. There is an excise tax on children's vaccines; this money goes into a pot and there is a commission that adjudicates compensation for children that are injured. The rationale for compensation has been well worked out, the system's working and the vaccine companies are shielded to a reasonable extent from liability and litigation. Another part of that law was actually an absolute disaster. It put in place a National Vaccine Program (NVP), with a Program Director named by the Assistant Secretary of Health who would report directly to the Secretary of Health and Human Services. That program never worked. It was supposed to coordinate the activities of the NIH and the CDC with the FDA and whoever else in the federal government was involved. The program was supposed to write a national plan, to coordinate in effect the whole industry. It never worked. The big agency heads were always more powerful than the guy who was trying to learn something.

The National Vaccine Plan was written by an interagency committee, but it contained nothing except pabulum. It had no measures, no muscle and no direction; it just had nice things to say about each agency. Congress finally repealed the initial program, and the residual compensation program is now at the CDC for a little while. It was a great attempt to solve our social problems with getting the vaccines that we need — and had tremendous unrealized potential.

I think the other great legislative failure was the Omnibus Budget Reconciliation Act of 1993 that set in motion the Vaccines for Children program. It threatened the vaccine industry from an economic point of view. The program was championed by the administration over the objection of those like Senator Bumpers who know the vaccine field. It's had a tremendous impact; I believe that it resulted in a very unfortunate polarization between the vaccine industry and the government over a bitterly contentious issue. The concern of the public health community is that a critical amount, approximately 40–60%, of the vaccine produced has to be purchased by the public sector and distributed to folks for whom the cost of the vaccine delivery and active care would preclude immunization.

Yet, unfortunately, under the Vaccines for Children program, states were buying vaccines under the federal program and making them available to the insurance industry. So the vaccine industry wound up subsidizing the insurance industry. Terrible legislation with a terrible impact. I'm sure nobody with a hand in that realized what they were doing. One effort that we're working on now is to get the health care and the medical insurance industries to ensure the purchase of the appropriate vaccines within their financial limits. The health care industry is very willing and is very aggressive in some ways in doing that; they are beginning to see the benefits. The big health care organizations do it very vigorously because they see populations that benefit. The smaller organizations would rather have their patients go to somebody else for vaccines. In this country we need an appropriate and cost-effective distribution of vaccine costs between the private and public sectors. We do not have that yet.

Conclusion

Three big issues in developing needed vaccines are: (1) vaccine production economics per se, (2) the aggregation of intellectual property required to produce optimal vaccines, and (3) the inability to plan at the national level.

It might be possible to deal with some of these issues in a consortium between the vaccine industry and the government — something like the one used to modernize computer chip manufacturing. To accomplish this, CEOs of all the big computer companies had to consider the plan and discuss it in some depth.

However, the cultures of various companies involved with vaccines are so competitive and so different that this may not be feasible. Large corporations can't figure out how to work together. Because of this and the failure of the government to get its act together, the public health system remains stuck with vaccines that are far below the level that we could potentially produce.

