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Expanded Programme on Immunization

FRAMEWORK FOR EVALUATING A VACCINE FOR THE EPI



World Health Organization
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Framework for Evaluating a Vaccine for the EPI

What questions need to be considered before the R&D group can recommend a vaccine be included into the EPI?

- * Priority of the Disease and Its Control
- * Characteristics of the Vaccine
- * Programmatic Feasibility
- * Vaccine Supply

1. Priority of the Disease and Its Control

Issues	Interaction with EPI	Questions to be Considered
1.1 Definition of the Problem	Priority given scarce resources?	What disease or condition is the vaccine directed against?
1.2 Magnitude of the Problem	Priority given scarce resources?	What is the morbidity/mortality of the disease in developing countries? How does this differ geographically?
1.3 Strategies to Address Problem	Fit with EPI?	How do the strategies for control differ for various environments?
1.4 Immunization versus Other Interventions	Priority given scarce resources?	How effective are other interventions? Would immunization have a substantial health benefit over other interventions?
1.5 Cost-Effectiveness	Priority given scarce resources?	What is the cost-effectiveness of using a vaccine? and of providing the vaccine through national immunization programmes?

2. Characteristics of the Vaccine

Issues	Interaction with EPI	Questions to be Considered
2.1 Immunogenicity 2.2/2.3 Efficacy 2.4 Duration of Immunity 2.5 Interaction with other Antigens	Schedule?? Fit with existing contacts? Fit with target group?	Efficacy / Immunogenicity / Duration as a function of age and target group in differing developing country conditions? Need for boosters? Interaction with other antigens?
2.6 Safety/ Adverse Reactions	Impact on populations perception of immunization?	Safety in developing country conditions? Trade-off between protection and adverse reactions? Interactions with other health problems?
2.7 Dose Route of Administration	Training? Equipment? Potential Coverage?	Dose response by age? Alternative routes of administration?
2.8 Storage Thermostability	Characteristics relative to existing EPI vaccines?	Thermostability / freezing point of vaccine? Shelf life and distribution implications? Physical space required in cold chain? Can the vaccine "go beyond" the cold chain?
2.9 Potential for Combination	Fit with EPI? Combine with EPI vaccines?	Can the vaccine be combined with other antigens?

3. Programmatic Feasibility

Issues	Interaction with EPI	Questions to be Considered
3.1 Impact on Immunization Programmes	Training Staff Management Equipment	How will including the vaccine affect the immunization system and overall capacity?
3.2 Impact on Distribution Systems	Management Equipment	How will existing distribution systems and local infrastructure need to be modified?
3.3 Cultural Acceptability	Impact on the populations perceptions of immunization?	Acceptability of controlling the disease? Acceptability of vaccine, route of administration, target group, adverse reactions?

4. Vaccine Supply

Issues	Interaction with EPI	Questions to be Considered
4.1 Technology Transfer	Will technology transfer strengthen the programme?	Is technology transfer feasible both from a technical and patent perspective?
4.2 Impact on Local Production	How will the impact on local production affect the EPI?	How will the new vaccine impact local production?
4.3 Adequate Global Supplies	Will there be enough vaccine to meet the needs of national immunization programmes?	Will there be adequate supplies given both local production and procurement? At what price? Will Unicef or another agency procure the vaccine?
4.4 Affordability	Is this the best use of scarce resources?	At what price is the vaccine affordable? What can be done to attain a price close to this point?

The work of the pharmaceutical industry, academic groups, the Programme for Vaccine Development (PVD), and the Children's Vaccine Initiative (CVI) is expected to result in the development of a number of newly licensed vaccines. As these vaccines become available, Ministries of Health, donors, and development agencies require information and recommendations for use of the vaccine in both industrialized and developing countries. The Expanded Programme on Immunization (EPI), through its Research and Development Group (R&D), has developed a framework which may be useful to both vaccine developers and vaccine users. The framework lists a series of questions which should be addressed as new vaccines are considered for introduction into public health use. Early consideration of these issues and questions by academic investigators, industry, regulators, agencies, donors and Ministries of Health may help to direct development efforts in ways which accelerate the production and use of these vaccines. This framework may be useful in initiating studies which facilitate the early introduction of new vaccines and in identifying remaining information gaps which need to be addressed.

In the past, research and development for new vaccines often focused on problems and conditions found in industrialized countries, and delays of many years occurred before the appropriate questions allowing use in developing countries were answered. Over the past decades, a network of national immunization programmes has been developed which delivers immunization to most of the world's women and children. The characteristics of this immunization network are not limitations to the introduction of new vaccines. However, vaccines which are compatible with the EPI vaccines, delivery schedules and vaccine distribution system will be relatively easy to deliver, while those which are not will require much greater financial and resource investments.

The usefulness of a generic research framework can be illustrated by the experience with several vaccines, particularly the lessons recently learned through the introduction of Hepatitis B (HB) vaccine into routine infant immunization programmes. HB vaccine was developed and licensed primarily for adult use in industrialized countries in 1982 and extensive research to determine the best ways to use this vaccine in developing country national immunization programmes took many years. The research was instigated by industry, government agencies, and academic research teams in a relatively uncoordinated way. A framework outlining the necessary tasks and research issues might have significantly streamlined the research and development process.

This paper is an effort to develop a generic framework which may be tailored for each vaccine. No attempt has been made to prioritise the points raised in the framework because the importance of various factors will differ from vaccine to vaccine. For example, use of one vaccine may be limited by its affordability, another by its immunogenicity in young children,

and a third by its side effects. For other vaccines, the magnitude of the disease burden may override limitations in the vaccine itself. Thus the relative weights of various factors cannot be generically determined, and the framework will be more useful in assuring that key issues are not overlooked.

The issues which need to be considered fall into four primary categories:

- * Priority of the Disease and Its Control
- * Characteristics of the Vaccine
- * Programme Feasibility
- * Vaccine Supply

1.0 Priority of the Disease and Its Control

1.1 What disease or condition is the vaccine designed to prevent?

Vaccines may be designed and tested for indications other than those of primary interest to the EPI.

HB vaccine was initially tested for its ability to control acute viral hepatitis and the chronic carrier state in high risk adult populations. It was then tested for its ability to prevent perinatal transmission from carrier mothers to their newborns. Finally, studies were designed to measure reduction of the HBV carrier state in cohorts of children in the general population, since HB vaccine in developing countries should be used as a routine vaccine for all infants to prevent the development of the carrier state and its sequelae, chronic hepatitis, cirrhosis and primary liver cancer.

Haemophilis influenza B vaccine was designed and tested for its ability to protect against meningitis, but pneumonia caused by this organism is a more important problem for many developing countries: the efficacy of this licensed vaccine to prevent pneumonia has not yet been established. Pneumococcal conjugate vaccines are being developed primarily to protect against otitis media in industrialized countries: its ability to protect against pneumonia in children in developing countries will be established at a later time, and may require that the composition of the vaccine be revised.

1.2 What is the magnitude of the problem in different countries? What is the health priority for control of this infection?

An in depth understanding of the magnitude of the disease problem is an important prerequisite for consideration by EPI. The extent and severity of the disease burden may differ in different countries, and should be an important factor in

determining the interest that governments and donors have in including the vaccine in national health programmes. However, the actual magnitude of a disease and the perception of its importance may vary.

Hepatitis B results in both acute hepatitis and in delayed hepatic cirrhosis and cancer. In the United States and Europe, the medical community and the public are primarily aware of the acute manifestations of infection. In Asia, the late manifestations of HBV were recognized by the medical community, the government, and the public as major public health problems, and HB control was given a high priority. In Sub-Saharan Africa, with an incidence and prevalence of HBV infection comparable to Asia, HBV infection is not perceived as a major problem in some countries. Because death from HBV infection occurs in adulthood and not childhood, some donors do not view its control as a priority.

Originally, health officials in many industrial and developing countries outside of Africa were very sceptical about the magnitude of the measles problem. Studies proving the morbidity and mortality levels of measles were needed to convince these countries about the need to control the disease. Now that measles is widely accepted as being a serious health threat, all national immunization programmes and donors are in agreement about the importance of controlling this problem.

1.3 How might the use of the vaccine and recommended strategies differ for various environments?

Strategies for use of a vaccine may differ in different epidemiologic and socioeconomic environments.

HB vaccine in many industrialized countries was initially recommended for high risk adult groups such as health care workers, sexually active individuals, IV drug users and dialysis patients. In many developing countries, where most adults have already been infected, immunization of infants against hepatitis B is a much better use of resources than adult immunization. It is interesting to note that many public health officials are coming to realize that only universal immunization of children or adolescents will control HB infection on a population basis even in industrialized countries.

Industrialized countries, with measles transmission primarily in older children, recommend that measles vaccine be given in the second year of life when maternal antibodies have fallen to undetectable levels and will no longer interfere with the vaccine. In developing countries, where a high attack rate may occur at younger

ages, it was necessary to accept a lower vaccine efficacy due to maternal antibody in order to minimize disease occurrence. Thus, the current recommendation in developing countries is that measles vaccine be given at 9 months of age.

1.4 How does immunization as a prevention strategy compare or combine with other interventions such as curative care?

The optimal strategy for disease control depends on a number of variables including the characteristics of the disease, the availability of vaccines and effective treatments, the availability of effective delivery systems, and the cost-effectiveness of each intervention.

Attempts to treat chronic HBV infections with interferon are extremely expensive and of very limited efficacy, so there are no practical alternatives to prevention through immunization.

While treatment for diarrhoeal disease and some acute respiratory infections are available, the attack rates and resulting morbidity and mortality may be sufficiently high to make a combined curative/preventive approach cost-effective.

Efforts to control leprosy through case management seem to be quite successful. If a vaccine is developed, the decisions to allocate resources between vaccine and treatment services would tend to favour the case management approach.

1.5 How cost-effective is the use of this vaccine to control the health problem?

Cost-effectiveness analysis allows one to compare the cost per impact achieved of various disease control strategies and resource allocation options. Decision makers at government levels are increasingly requiring "cost effectiveness" and "benefit cost" analyses before they will consider funding a programme. Sensitivity analysis can help measure the relative importance of different assumptions or variables such as disease incidence rates or vaccine price. If a vaccine is effective against a serious disease, there will be some vaccine cost at which the vaccine will be "cost effective" or "cost saving" for any incidence rate. Cost effectiveness and benefit cost analyses are not generic because of widely differing values of such variables as medical treatment costs, lost wages, life expectancy and indirect costs of the disease. Whether a "cost effective" intervention is affordable is a separate but obviously important issue.

For HB vaccine cost effectiveness analysis has shown that a chronic carrier can be prevented in a developing country for approximately \$40 at a vaccine cost of \$1 per dose. Even though the vaccine price is higher than the other EPI antigens, the "effectiveness" makes this intervention as "cost effective" as other EPI vaccines.

Analysis comparing the cost-effectiveness of leprosy control through case treatment versus immunization (assuming a vaccine is developed) has shown that immunization would only become more cost-effective than case treatment when the disease incidence rate is greater than 1/1000.

2.0 Characteristics of the Vaccine

2.1 What is the immunogenicity of the vaccine as a function of age? Can the vaccine be given at birth?

Immunogenicity can be measured by the proportion of subjects who develop protective immunity following immunization and the magnitude of these responses. Depending on the nature of the vaccine itself, it may be immunogenic at birth, it may not be immunogenic until passively acquired maternal antibody wanes, or it may require further maturation of the immune system.

HB vaccine induces anti-HBs antibody at birth, which is known to be protective. Polysaccharide based vaccines are usually not reliably immunogenic before 18-24 months of age, but significant morbidity from bacterial pathogens with polysaccharide capsules occurs before this age. Coupling the polysaccharide to carrier proteins has made some of these antigens immunogenic as early as two months of age. Live attenuated measles vaccines, on the other hand, are affected by maternal antibodies and are maximally immunogenic only when these antibodies fall to non-inhibitory levels, yet a significant amount of morbidity and mortality occurs before the vaccine can be administered.

2.2 How effective will the vaccine be in preventing infection or disease?

When vaccines are being developed, the level and type of protection conferred by the induced antibodies is not always clear. Efficacy studies may be needed to prove that the vaccine will protect humans against the disease.

Killed V. cholera vaccines injected into humans induces neutralizing IgG type antibodies. However, the site of action of the pathogen is the intestinal mucosa, and newer oral vaccines are being developed to stimulate both mucosal (intestinal) immunity via secretory IgA, and circulatory immunity. These vaccines may be more effective than the older injected vaccines.

It is not known which antibody induced by the whole cell pertussis vaccine is protective. The newer acellular pertussis vaccines must be tested for efficacy in humans because there are no data to correlate the antibody response induced by these vaccines to protection against disease.

2.3 Is the vaccine protective when given after exposure to the disease?

Vaccines directed against diseases with long incubation periods may have efficacy even when given after exposure to the pathogenic organism. HB vaccine may be given in either post-exposure or pre-exposure situations. Infants born to HB carrier mothers who are also positive for the HBeAg have a 70% to 90% chance of becoming carriers (perinatal transmission). HB vaccine, even when administered on the day of birth, is given to most of these children after exposure to the virus. The vaccine is 75% to 90% effective in preventing the carrier state in these infants. Infants of non carrier mothers, on the other hand receive vaccine well before exposure to the virus, and in these children, the efficacy is often measured at 95%.

2.4 What will be the duration of immunity induced by the vaccine? Will booster doses of vaccine be required to provide the required level of protection?

The duration of immunity of most vaccines is not well understood but it is critically important for the EPI, especially because it is not possible to deliver booster doses of vaccine years after primary immunization in many countries.

The belief that live attenuated vaccines would provide lifelong immunity comparable to wild type infection is being questioned for live attenuated polio and measles vaccines. In contrast, the concept that killed vaccines provide only short term immunity is being challenged by HB vaccine, where protection against clinical disease and development of the carrier state persists years after measurable levels of circulating antibody have waned. Circulating antibody was believed to provide protection against repeated HB infection, but now a number of investigators believe that circulating memory cells are the repository of long term immunologic memory, and because of the long incubation period of the disease, exposure to the virus (or to a booster dose of vaccine) induces appropriately primed memory cells to multiply and produce antibody in enough time to abort infection and prevent the development of disease or the carrier state. How long protection from this mechanism might last is unknown (we have only ten years experience with this vaccine), but it may persist for a prolonged period of time making booster doses unnecessary.

2.5 Will the vaccine interact with other EPI antigens?

It is of primary importance to document that the candidate vaccine will not adversely effect the immune response to existing EPI antigens, and conversely, that the EPI antigens will not effect the immune response to the candidate vaccine.

This has been well studied for HB vaccine which would be delivered at the same contact as DPT. HB does not adversely affect the efficacy of the diphtheria, pertussis and tetanus antigens. However, studies of the simultaneous administration of polio and rotavirus vaccines indicate that there may be significantly detrimental interaction between these two vaccines.

2.6 Is the vaccine safe enough for routine immunization? Is there a favourable trade-off between adverse reactions and benefits of immunization?

All vaccines induce adverse reactions in some recipients, if only from the alum adjuvant (which seems to be the case with HB vaccine) or preservative. Side effects which may be tolerated in some situations may be intolerable for mass immunization.

Older rabies vaccines were quite reactogenic, but were tolerated after a bite from a potentially rabid animal: they could not have been considered for mass immunization. Ironically, some vaccines (eg whole cell pertussis vaccine) have been the victim of their own success, controlling a serious disease only to have the public in some countries raise concern about adverse reactions many fold less serious than the disease.

2.7 What is the optimal dose and route of administration.

A given vaccine from different producers may induce different levels of immunity, and producers and national control authorities may recommend different doses of vaccine.

HB vaccine is not a generic product, and vaccines from various producers induce different levels of antibody per microgram of antigen. This can lead to great confusion on the part of consumers, which is not helped by the advertising and marketing efforts of competing manufacturers.

The optimal route of administration must also be established through careful study. In general, oral routes would be preferable as they are simpler and cheaper to administer, but OPV is the only vaccine which is administered by this route. The route of administration may also have important implications for the dose required for seroconversion.

HB vaccine, which should be administered intramuscularly, provided two useful lessons in this area. After licensure of HB vaccine in the US, reports of sub-optimal seroconversion were reported from a number of hospitals. Upon investigation, hospitals delivering vaccine into the buttock had much lower levels of seroconversion than those which had delivered vaccine into the deltoid. Vaccine delivered into the buttock is usually delivered into lipoid tissue instead of muscle, and is not a true IM injection.

Because of the initial high price of HB vaccine, many investigators studied the use of small intradermal doses of vaccine. Although the percentage of individuals seroconverting to anti-HBs was high, the geometric mean concentration of antibody was lower, and the intradermal route proved painful to infants, who have a very thin dermal layer. Intradermal vaccine was also both difficult to administer under field conditions and did not achieve good protection against perinatal infection.

An unfortunate incident involving use of intradermal rabies vaccine in US Peace Corps volunteers in Africa has also reduced enthusiasm for this route of administration. Although intradermal administration seemed immunogenic in veterinary students, serologic investigation of the volunteers following the rabies death of an immunized volunteer showed that fewer than half had detectable antibody.

2.8 What is the thermostability, freezing point and shelf life? Can the vaccine go "beyond" the cold chain?

The relative thermostability of vaccines (compared to current EPI vaccines) is critical because the vaccine distribution system, a cornerstone of the EPI, was fitted to the existing vaccines. While the cold chain can and will be adapted to new vaccines, significant changes could be expensive and may slow the introduction process.

The current cold chain parameters are set by the thermostability of oral polio vaccines. This vaccine loses its potency after 1 day at 37°C. WHO is currently searching for methods to increase the thermostability of polio vaccine in hopes of simplifying the storage, transport and administration of vaccines.

Vaccines that will not tolerate freezing are also a problem. The constituents of DPT change their physical properties upon freezing, flocculating out of solution and often settling to the bottom of the vaccine container. In some vaccine programmes, this flocculation of the active ingredients has resulted in non-effective immunization.

Less stable vaccines, vaccines with a short shelf life, or vaccines that could be destroyed by the thermal conditions of the cold chain would be very difficult to integrate into the system without major effort and expense.

More stable vaccines, on the other hand, would be ideal, since the cold chain is one of the major constraints to vaccine delivery.

HB vaccine is quite heat stable and can resist several weeks or months at room temperature without loss of immunogenicity. This ability has been exploited in one study in Long An County, China, where traditional birth attendants were given vaccine to store at home without refrigeration and taught to deliver vaccine at home births, allowing early immunization of infants to improve the efficacy in preventing perinatal transmission. However, HBV vaccine inactivates upon freezing.

2.9 Can the vaccine be physically combined with other EPI antigens.

Multiple antigen vaccines requiring fewer doses are the goal of the Children's Vaccine Initiative and of many investigators in the field of vaccine development. Any new antigen which can be combined with current EPI vaccines such as DPT will have obvious advantages in reducing the number of injections, syringes, training and administrative costs, and in the vaccine distribution system.

Initial attempts to combine HB vaccine with DPT showed a decrease in anti-HBs antibody concentration in recipients who received vaccine which had been combined in one vial compared to subjects receiving the vaccines simultaneously but in separate sites. Efforts are under way to prepare successful DPT-HB vaccines as well as DPT combined with other antigens, such as HiB conjugate vaccine.

A similar situation occurred following initial mixing of inactivated polio vaccine with DPT. It was found that the preservative in the DPT, thimerosal, rendered the IPV impotent. When another preservative, phenoxylphenol, was used, the IPV retained its activity.

3.0 Programme Feasibility

3.1 How will including the vaccine in national immunization programmes affect the immunization system and its overall capacity?

EPI's purpose is to ensure the delivery and administration of effective vaccines and future vaccines may differ substantially from those currently delivered. However, the closer a vaccine fits to the characteristics of current EPI vaccines, the easier it will be to introduce. Proponents of all new vaccines and interventions will argue that their new

intervention will "strengthen the EPI", but a realistic assessment is in order. Will the vaccine require additional contacts with the immunization system? Will additional staff be needed? Will the national immunization programmes be required to establish contact with an age group not currently reached?

HB vaccine can be integrated into EPI programmes without additional contacts or additional personnel.

If a vaccine against HIV were developed and targeted at adolescents, delivery of the vaccine would require large investments into the health infrastructure of many countries.

3.2 How will existing distribution systems and local infrastructure need to be modified?

This is extremely important, since requirements for additional cold chain equipment can be quite expensive, and could delay introduction of a new vaccine.

HB vaccine, being more expensive than other EPI vaccines, is usually ordered in fewer doses per vial than other vaccines to avoid wastage, increasing the volume needed to store it. In addition, many manufacturers packaged the vaccine very inefficiently, putting individual small vials in large boxes. EPI has issued proposed standards for packaging and shipping that will greatly improve this situation. Modelling done by EPI on cold chain volumes indicates that most countries should be able to absorb HB vaccine without additional equipment, but that central storage facilities in some countries may be strained by addition of this vaccine.

3.3 How acceptable will the vaccine be in different cultures?

The acceptance and use of the vaccine could be influenced by a variety of cultural factors such as the perceived importance of controlling the disease, of immunizing the particular target group and of certain vaccine characteristics.

Plasma derived HB vaccine was interpreted by certain religious groups to be a blood product and therefore unacceptable, while other members of these same religious groups had no problems accepting the vaccine. Rumours of sterilization following TT immunization has hurt programmes in several countries. Whole cell pertussis vaccine is not accepted in several countries because of perceived side effects that were not acceptable to many parents in the population.

4.0 Vaccine Supply

4.1 Is technology transfer to developing countries feasible and practical?

Many countries produce the EPI vaccines, so considerable technology transfer has taken place, but the quality of much of this vaccine is unknown. There is concern about the difficulties in ensuring consistent monitoring of quality control by independent and competent regulatory authorities.

Technology transfer for plasma derived HB vaccine is feasible and has been achieved for China, which will produce up to 45 million doses in 1992. Transfer of recombinant DNA technology to produce yeast derived HB vaccines is much more complex, and although there are a few projects in progress, no developing country currently produces DNA recombinant HB vaccine. Various production sharing schemes are being considered for more complex vaccines.

4.2 How will the new vaccine affect local production?

In countries with local production capacity, it is important to understand how the local industry will react to a new vaccine or production process. The industry could produce and use the new vaccine by upgrading or engaging in production sharing arrangements such as importing bulk and mixing, filling and finishing in the country. Conversely, the industry could choose to ignore the new technology and continue production and use of the older generation vaccine. Finally, the government or a donor could choose to import the new vaccine and discontinue local production.

The advent of DNA recombinant HB vaccines led some countries to drop plans to produce plasma derived vaccine. This may have led to increased costs in some countries. Many countries produce DPT with a whole cell pertussis component locally. Acellular pertussis vaccines are much more difficult and expensive to produce, and may not be feasible for local production in some countries. If local production ceases, this may lead to even greater donor dependence. Local production of combined vaccines such as DPT-HB vaccine or DPT-HiB vaccine would require the development of a generic process to combine vaccines, and this may or may not prove to be feasible, since DPT vaccines vary widely in purity and adjuvant concentration.

4.3 Will vaccine supplies be adequate for global needs?

The global vaccine demand must be estimated and compared to the global supply available through local production and international procurement.

High titred Edmondson Zagreb measles vaccine could not be produced in adequate quantities for international distribution. Production of several hundred million doses per year of plasma derived HB vaccines may have been problematic. Yeast derived DNA recombinant vaccines can be produced in virtually unlimited amounts using fermentation technology.

4.4 At what price is the vaccine affordable? What can be done to attain a price close to this point?

There is a vaccine price at which any effective vaccine against a serious disease will be "cost effective", but it may not be "affordable".

HB vaccine initially cost more than \$50 per infant for a three dose series, and integration into routine infant immunization was not considered feasible at that price. The price is now approximately \$3 to \$5 per paediatric series in developing countries, and 41 countries are able to obtain vaccine for their children. However, many governments and donors with limited funds still do not find the current price affordable and so cannot introduce this vaccine into their immunization programmes. HB vaccines were initially developed by large European and North American pharmaceutical companies that targeted vaccine to health care workers at a high price. Vaccine price came down substantially in the developing world when countries such as Korea began to market the vaccine and market competition began.

The cost of developing, producing and marketing new vaccines may be very high, and manufacturers in industrialized countries will include these costs, plus the costs of developing other products which never reach the market, in the price of the vaccine. Newer vaccines will not be available at the cost of the traditional EPI vaccines, which are all older products whose price to EPI is subsidized by sales at a higher price in industrialized countries. It has taken 10 years for the price of HB vaccine to fall to the level where it is affordable in some countries, and the price is still much higher than that of the other EPI antigens. Groups such as the CVI are looking for mechanisms to allow developing countries to use newer vaccines without waiting decades to obtain them.

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