

Translational Research to Assist Policy Decisions about Introducing New Vaccines in Developing Countries

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ABSTRACT

Few new-generation vaccines have found their way into public-health programmes for the poor in developing countries, and for those that have, delays of years or even decades after their licensure and introduction in industrialized countries have been the rule. Financial constraints and political obstacles have played major roles in delaying the introduction of the vaccines. Also contributing to this situation has been a dearth of needed research. While past analyses have identified inadequate support for conducting Phase 1 studies as an obstacle, other types of translational research are also needed. Vaccines may perform less well in impoverished populations in the developing world than in more affluent populations. Consequently, Phase 2 and Phase 3 trials of new vaccines in developing countries are a second essential type of translational research needed for the introduction of vaccines in developing countries. Moreover, even for vaccines that have performed well in pre-licensure human trials in developing countries, doubts often remain about whether the local disease burden justifies introduction of vaccine, whether the vaccine will be cost-effective, and whether introduction of vaccine will be programmatically feasible, acceptable, and financially sustainable. Because these residual doubts constitute obstacles to the introduction of vaccine, a third type of translational research is needed to provide this evidence required for policy. In this paper, these three types of translational research are illustrated with projects being undertaken in the Diseases of the Most Impoverished Programme. The Programme is conducting translational research to accelerate the rational introduction of new vaccines against cholera, shigellosis, and typhoid fever in developing countries affected by these diseases.

Key words: Vaccines; Vaccine development; Bacterial vaccines; Communicable diseases; Research; Developing countries

INTRODUCTION

The world is in the midst of a revolution in vaccine development, which is yielding a wide array of new approaches to vaccines and an increasing number of vaccines against newly-targeted diseases. Despite this, the movement of introduction of new and improved vaccines into the public-health programmes of develop-

ing countries has been painfully slow (1). This is most unfortunate since many of these new-generation vaccines, such as those against diarrhoea, meningitis, and pneumonia, are targeted against diseases that are major public-health problems in developing countries.

Much has been written about the scientific challenges of vaccine discovery and about strategies to improve the process of discovering new vaccine candidates. The financial hurdles and programmatic obstacles that impede the introduction of new vaccines in developing countries are also well-known. Less well-appreciated is the fact that, even for the existing vaccine candidates, there may be other formidable scientific challenges that can impede their introduction into

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public-health programmes in developing countries. The research agenda that address these challenges, which we term translational research, or research to translate experimental vaccine candidates into practical tools that are used in the public-health practice, is the subject of this issue of the Journal of Health, Population and Nutrition.

CLINICAL PARADIGM FOR EVALUATING VACCINES FOR LICENSURE

To place the rationale for translational research into context, it is helpful to describe the phases of clinical evaluation of vaccine candidates prior to licensure (2-3). Phase I trials are the initial human studies of a candidate; these are conducted when the candidate has shown promising results in pre-clinical evaluations. These trials are typically small in size (e.g. ca. 10-20 subjects), enroll healthy adult subjects, and are designed primarily to evaluate whether the vaccine is associated with frequent adverse effects. Phase 1 trials also typically evaluate other vaccine effects, such as immune responses and vaccine excretion (for live vaccine candidates) and may be used for determining an optimal dose and regimen for the vaccine candidate. Vaccine candidates found to be suitable in Phase 1 trials may be tested in Phase 2 trials. Phase 2 trials are distinguished by their larger sample sizes (often in the range of several hundred subjects); by their ability to evaluate, in a statistically meaningful fashion, immune responses and less common adverse reactions; and their eventual inclusion of subjects in the populations and age groups that will be the ultimate targets for the vaccine in public-health practice. Phase 2 trials may also measure excretion and transmissibility of live vaccines. Although Phase 2 trials are not typically designed to measure vaccine protection against the target infection, special types of Phase 2 trials, occasionally termed Phase 2b trials, are sometimes conducted to measure vaccine protection against experimental challenges with the target pathogen. Finally, for candidates found to be suitably safe and immunogenic in Phase 2 trials, Phase 3 trials may be mounted. The distinctive feature of Phase 3 trials is that they measure vaccine protection against naturally-occurring infections in populations at risk. Phase 3 trials are usually quite large, often enrolling thousands of subjects and are always conducted in the populations and age groups to be targeted by the vaccine. Because of their large sizes, Phase 3 trials are usually capable of detecting

rather uncommon adverse events associated with vaccination. Moreover, because Phase 3 trials measure both immune responses to vaccination and vaccine protection, they may be able to correlate the two and thus to derive immunological correlates of protection. Phase 1 trials may be conducted in a controlled or uncontrolled fashion; Phase 2 and Phase 3 trials conventionally employ double-blind, randomized, controlled trial designs.

TRANSLATIONAL RESEARCH: OVERCOMING HURDLES TO INTRODUCTION OF NEW VACCINES

Translational research to accelerate the introduction of an already-developed vaccine candidate into public-health programmes in developing countries addresses three types of scientific challenges. First, a vaccine candidate may languish on the laboratory shelf without an opportunity to be tested in humans. This developmental impasse is most notorious for orphan vaccines, targeted to diseases that are of little or no interest to populations in industrialized countries and having limited potential profitability for vaccine producers. Examples of such vaccines include those directed against leishmaniasis, hookworm disease, and schistosomiasis. Because such diseases primarily affect developing countries and since affluent travellers to developing countries are not at high risk of contracting these diseases, there is little economic incentive for industry to undertake expensive clinical development programmes for these vaccines.

Second, even for vaccines that are of interest to populations in industrialized and less-developed countries alike, there may be interest in and funding for human studies only in industrialized countries, where the most profitable markets are located. Indeed, conduct of parallel clinical development pathways in industrial and developing settings risks delays in licensure in markets of industrialized countries, with loss of income generation. This creates a problem for developing countries because the results of studies done in populations of industrialized countries do not always predict the performance of a vaccine in populations of developing countries. Such has been the case for both early-generation vaccines against rotavirus (4-6) and against *Haemophilus influenzae* type b (7-8), which were highly protective in children of industrialized countries but poorly protective in children of developing

settings. Too often in the past, studies have ultimately been done in developing countries, but only many years after a vaccine's licensure in industrialized countries, creating an unacceptable delay in vaccine introduction even when such trials were successful (9).

Third, even if a vaccine has been shown to be safe and protective in Phase 3 trials in developing countries, policy-makers may still have uncertainties about whether an adequate case can be made for introducing the vaccine into public-health programmes in their countries. This is because the evidence provided by pre-licensure evaluations, even those done in developing countries, typically fails to address many practical questions about implementing a new vaccine in real-life programmes, which must be answered before a decision can be made to introduce a vaccine (10). The insufficiency of this evidence from the required downstream research constitutes the third scientific hurdle.

Overcoming these three types of hurdles requires three types of translational research (11-12). The first scientific hurdle requires conduct of initial human studies (Phase 1) of promising vaccine candidates. The second scientific hurdle requires Phase 2 and Phase 3 studies in developing-country settings, ideally conducted in parallel with evaluations in industrialized countries. And the third scientific hurdle requires, for vaccines that have proven safe and effective in Phase 3 trials in the developing world, generating epidemiological, clinical, economic, behavioural and policy evidence sufficient to make an adequate case that the introduction of a new vaccine into public-health programmes in a developing country is rational, feasible, acceptable, and affordable.

Central to overcoming each of these three hurdles is funding for the needed research. In the past several years, the public sector has become increasingly willing to provide funding for such research, thus alleviating much of the risk that would otherwise have fallen upon vaccine producers. The recent availability of major funds from the public sector, including the Bill and Melinda Gates Foundation, the Global Alliance for Vaccines and Immunization (GAVI), and governmental funding from the industrialized world, has opened new opportunities for the accelerated development and introduction of new vaccines against diseases afflicting developing countries.

In the remainder of this paper, we provide examples of how a major programme of translational research

and technical assistance, the Diseases of the Most Impoverished (DOMI) Programme, supported by the Bill and Melinda Gates Foundation and coordinated by the International Vaccine Institute (IVI), is addressing the challenges of overcoming these three hurdles to accelerating the rational introduction of new-generation vaccines against cholera, shigellosis, and typhoid fever into programmes for the poor in countries affected by these diseases.

DOMI PROGRAMME

Background, rationale, and objectives

As global attention has focused increasingly on vaccines for three major infectious disease problems of the developing world—HIV/AIDS, malaria, and tuberculosis, some diseases of importance have failed to receive the attention warranted by the burdens of morbidity and mortality imposed upon populations residing in developing countries. A good example is the collection of infections affecting the gastrointestinal tract and causing diarrhoeal illnesses and enteric fever, which continue to exact a high toll of mortality, particularly in developing countries (13). Three bacterial enteric infections—cholera, shigellosis, and typhoid fever—are thought to account for nearly two-thirds of these deaths.

Interestingly, the situation is very different for new-generation vaccines against these enteric infections than for those against HIV/AIDS, malaria, and tuberculosis, for which new-generation vaccines are now being developed and are years away from potential implementation in public-health programmes. For cholera and typhoid fever, several new-generation vaccines exist and are licensed for use in travellers from wealthy countries, but are not being used to any appreciable extent in programmes for the poor in the developing world. Moreover, experimental vaccine candidates and novel approaches to construction of vaccine candidates exist for all three diseases, but because these vaccines have limited commercial potential, vaccine manufacturers have been unwilling to invest the resources needed to push these products forward to licensure.

The opportunities for the introduction of the existing new-generation vaccines against cholera and typhoid fever in the near-term and for the future introduction of improved, newer vaccines against all three diseases provided the basis for the DOMI Programme.

For the existing vaccines, DOMI is focusing on generating an evidence base for the introduction of oral, killed whole-cell-based vaccines against cholera and of Vi polysaccharide vaccine against typhoid fever. Both the vaccines are safe and moderately effective (14-16) and constitute major improvements over older-generation, parenteral whole-cell vaccines, which were abandoned as public-health tools (17-18). Moreover, both the vaccines are already being produced by international and local producers and can be produced at a low cost.

In addition, DOMI is evaluating the clinical performance of experimental vaccines against cholera, shigellosis, and typhoid fever in endemic settings, sponsoring the accelerated development of a new-generation candidate against *Shigella* and is generating evidence for policies to introduce present and future vaccines against all three diseases. At present, the research of the DOMI Programme is focusing primarily on countries in Asia, although the work has recently begun to extend to sub-Saharan Africa.

Partners

Early in the DOMI Programme, it was recognized that its success depended on forging partnerships with all major stakeholders with interests in new vaccines against cholera, typhoid fever, and shigellosis. A key partner is the World Health Organization, and DOMI has joint secretariats at IVI headquarters in Seoul and at WHO headquarters in Geneva. Other important partners include: Ministries of Health in the principal DOMI partner countries (Bangladesh, China, India, Indonesia, Mozambique, Pakistan, Thailand, and Viet Nam); investigators in the partner countries; international experts on vaccines for cholera, typhoid fever, and shigellosis; and vaccine producers in both industrialized and developing countries (the latter are sometimes referred to as 'local' producers).

An important consideration for accelerated introduction of a vaccine is conducting translational research within the existing national infrastructure of developing countries for which the research is intended. While reliance on industrialized-country researchers and research institutions may be expedient in the short-term, the research will be much more likely to be communicated to national decision-makers and to influence policy if it is done 'within the system' and if countries feel ownership of the research. This approach to research has been a cornerstone of the DOMI Programme.

How DOMI's translational research is addressing the first hurdle

Expert advisors to the DOMI Programme underscored the fact that, of the three DOMI diseases, the barrier to movement of vaccines from pre-clinical to clinical testing of vaccines was the greatest for shigellosis. While a number of candidates for shigellosis have been developed, none is being taken to licensure by industry due to the limited anticipated profitability of *Shigella* vaccines.

The experts also noted that, while a number of technologies for vaccine development and production have been explored for *Shigella* vaccines, including both molecularly-engineered subunit vaccines and genetically-attenuated live strains, insufficient attention had been devoted to an earlier-generation technology, ribosomal vaccines, in which polysaccharide-ribosomal complexes are isolated from *Shigella* organisms after disruption and ultracentrifugation. Results of animal studies of parenterally-administered ribosomal vaccines, done in the 1970s and 1980s, demonstrated that these vaccines were safe, immunogenic, and protective in animal models (19). Interestingly, these studies suggested that the vaccines elicit T cell-dependent immune responses to the polysaccharide component, analogous to responses to polysaccharide-protein conjugate vaccines. Moreover, patents do not protect the production technology for *Shigella* ribosomal vaccines, and the simple methods of production could be done at a low cost. Because of these features, in the 1980s, the Walter Reed Army Institute of Research undertook production of clinical lots of these vaccines for human testing. However, because early lots of the vaccine had unacceptable levels of contamination by endotoxin, the programme was terminated, and the vaccine was never evaluated in humans.

DOMI's experts on *Shigella* vaccines believed that this approach had been dropped prematurely and should be pursued, especially because *Shigella* ribosomal vaccines, if proven safe and effective in humans, would be feasible and cheap to produce by qualified local producers in *Shigella*-endemic countries. In the DOMI Programme, vaccine process research scientists at IVI, in collaboration with scientists at the Institut Pasteur, Paris, France, are undertaking process research to produce a clinical-grade lot of *Shigella flexneri* 2a ribosomal vaccine. The approach adopted by these scientists is novel in that it uses a source strain

genetically attenuated by an msbB mutation that partially detoxifies the lipid A of the endotoxin of the organism (20), and it is employing more modern methods to remove lipopolysaccharide than those earlier used at the Walter Reed Army Institute of Research. Assuming that this pre-clinical development programme is successful, DOMI will produce a clinical-grade lot of the prototype and will move the candidate into Phase 1 human studies.

How DOMI's translational research is addressing the second hurdle

Several experimental vaccine candidates are available for each of the three DOMI diseases. As already mentioned, commercial producers have been reluctant to sponsor the clinical development of vaccines against *Shigella*. However, the U.S. Army sponsored the production of a genetically-attenuated, live oral *S. flexneri* 2a candidate, SC602, developed by the Institut Pasteur. Because of promising results when the vaccine was given to North American adults (21), evaluation of the vaccine was moved to Bangladesh, at ICDDR,B: Centre for Health and Population Research. DOMI co-sponsored, together with USAID and the U.S. Army, a dose-ranging trial of a single dose of this vaccine in young Bangladeshi children. This study, which followed several trials in older age groups of Bangladeshis, was of particular importance because young children would constitute a logical target group for immunizing against *Shigella* in this setting. The trial in young children showed the vaccine to be safe, but poorly immunogenic, at least as manifested by rises in serum and faecal anti-LPS antibodies, at all tested doses. This study highlights the importance of evaluating *Shigella* vaccines in target populations in endemic areas, in whom responses might differ from those seen in populations in the industrialized world.

Another vaccine targeted by DOMI is Peru 15, a genetically-attenuated, live oral vaccine against cholera developed at Harvard University (22). Despite promising results in North American volunteers, the vaccine languished for years without evaluation in a cholera-endemic country until the DOMI Programme launched a series of Phase 2 trials of the vaccine with investigators at ICDDR,B. These trials, which are also being conducted in collaboration with Avant Immunotherapeutics, are now ongoing in sequential groups of progressively younger volunteers, and initial results have been promising. If these results are borne out by

the complete series of studies in Bangladesh, DOMI plans to take the vaccine forward to one or more Phase 3 trials.

Both subunit vaccines and genetically-attenuated strains have been developed against typhoid fever. Among the latter, the live oral vaccine, ZH9, has yielded very promising results as a single-dose vaccine in both inpatient and outpatient studies done in the United States and the United Kingdom (23). Because of these encouraging results, DOMI is working with Microscience in the United Kingdom, the developer of this vaccine, and the Wellcome Tropical Disease Unit in Ho Chi Minh City to launch Phase 2 studies of this vaccine in a typhoid-endemic population in Viet Nam. If the results of these studies are promising, DOMI will move forward with a Phase 3 trial of the candidate in a typhoid-endemic setting.

How DOMI's translational research is addressing the third hurdle

The vast majority of translational research being conducted by DOMI focuses on the third scientific challenge: providing evidence to policy-makers that will help them make rational, near-term decisions about whether to invest in introducing currently-available, licensed vaccines against cholera and typhoid—oral, killed whole-cell vaccines and Vi polysaccharide vaccine—into programmes for the poor in their countries, and about longer-term decisions about introducing future improved vaccines against all three diseases as they become available (24).

A major challenge of these research programmes was to design them in a way that was responsive to the needs of national policy-makers in endemic countries, since these policy-makers constitute the major audience for the research findings of DOMI. At its inception, the DOMI Programme conducted a survey of policy-makers and opinion leaders in Bangladesh, China, India, Indonesia, Pakistan, Thailand, and Viet Nam. In all, approximately 200 policy-makers participated in face-to-face, semi-structured interviews. The interviews were conducted with personnel in the Ministries of Health, Ministries of Finance and National Regulatory Authorities; academic leaders in infectious diseases; and local vaccine producers. Results of these interviews showed that the policy-makers needed four types of information to make decisions about the introduction of new vaccines against cholera, shigellosis, and typhoid fever into programmes for the poor in their countries.

1. Acquisition of epidemiological data on the burden and distribution of diseases in their populations

Policy-makers emphasized the need for more contemporary data on the burden and distribution of cholera, shigellosis, and typhoid fever in their countries. To collect epidemiological data, DOMI has launched several prospective, large-scale disease-burden studies of cholera, shigellosis, and typhoid fever in defined populations and has also undertaken meta-analyses of the results of existing published and unpublished studies. The latter have been placed on a special website for use by policy-makers. To enhance the interpretability and policy impact of these studies and to generate comparative evidence, DOMI is conducting prospective studies in a coordinated fashion in different countries with common clinical and microbiological diagnostic protocols. These analyses are also helping define the most appropriate vaccine-introduction strategy, both in terms of the targeted population (e.g. infants, at-risk groups) and programmatic administration (e.g. Expanded Programme on Immunization, repeated mass immunizations, and selective immunization). Finally, epidemiological studies of DOMI on the phenotype distribution of target pathogens are revealing data that will be pivotal for future vaccine-development options. For example, epidemiological studies of DOMI have shown a substantially greater-than-expected diversity of *Shigella* species and serotypes, indicating the need for a broad 'cocktail' of different *Shigella* organisms for a vaccine that will have an important epidemiological impact.

2. Pilot demonstration projects in real-life conditions of licensed oral killed whole-cell cholera and Vi polysaccharide typhoid vaccines

Policy-makers considered demonstration projects to be critical for generating evidence on programmatic feasibility, expense, acceptability, and impact of vaccine in real-life situations. To provide this evidence, DOMI is conducting multiple demonstration projects of these vaccines. Several of these projects are designed as cluster-randomized effectiveness trials to provide information on the protective impact of vaccination and the feasibility and acceptability of vaccine delivery, assessed by ethnographic studies done both before and after vaccination (10). For Vi vaccine, four large-scale effectiveness trials are being conducted in China, India, Pakistan, and Viet Nam, using study designs standardized across these sites. In addition, one non-controlled

demonstration project has been conducted in school children in Jakarta. As in the DOMI disease-burden studies, the coordinated, multi-country approach will provide important comparative data for use by policy-makers on a regional basis.

3. Analyses of the economic impact of introducing oral killed whole-cell cholera and Vi typhoid vaccines into public-health programmes

Policy-makers queried in the survey also emphasized that data on the economic ramifications of vaccine introduction were critical to their deliberations about whether or not to introduce the oral killed whole-cell cholera and the Vi typhoid vaccines into public-health programmes. Several types of economic evidence are needed. First, it is necessary to know the economic cost that these diseases impose on a population. Remarkably, empiric data on costs of illness, measured in real patients with confirmed diagnoses, are virtually absent for cholera and typhoid in developing countries. Second, it is necessary to know the combined costs of purchase and delivery of vaccine, measured in real-life programmes. Third, the balance between vaccine costs and vaccine impact must be estimated in economic analyses. The DOMI Programme has responded to these needs by launching studies of institutional and private costs of illness in conjunction with its prospective disease-burden studies, by measuring costs of purchase and delivery of vaccine in vaccine-demonstration projects, and by conducting formal cost-effectiveness studies, making use of empiric data collected in the field on disease incidence, impact of vaccination, costs of purchase and delivery of vaccine, and costs of illness.

Regardless of the results of cost-effectiveness analyses, vaccines will not be introduced unless introduction is economically sustainable. To address this need, DOMI is also undertaking analyses of economic consequences of different innovative channels of vaccine introduction, including introduction of new vaccines at higher prices into the private sector of developing countries to subsidize sales of low-cost vaccines to programmes for the poor.

4. Assessment of community and providers' perceptions

Policy-makers expressed a need for more information on perceptions about the importance of these diseases, the need for vaccinating, demand for vaccine, and willingness to pay within countries. These factors are

important, since amidst the current plethora of new vaccines being developed for inclusion in the public-health programmes in developing countries, it may not be possible to finance delivery of cholera and typhoid vaccines with scarce national financial resources, even when supplemented by contributions from external donors, and some user-fees may need to be imposed. DOMI has responded to this need by conducting various sociobehavioural and economic studies in the field. The studies, done in conjunction with the prospective disease-burden and demonstration projects, have assessed perceptions of populations regarding the importance of cholera and typhoid as public-health problems, the adequacy of current control measures for these diseases, the desire for vaccines against them, the characteristics of a vaccine that would make it acceptable, and the willingness to pay out of pocket to receive the vaccines. An important feature of these studies is that they have been done in two distinct populations: impoverished communities, which would be the primary target of public-health use of these vaccines, and middle-class communities. The latter are being surveyed because of the likely need to subsidize low-cost vaccines for the poor by the profits gained from higher cost sales to the more affluent segments of society.

Other considerations for programmes designed to accelerate rational introduction of vaccines in developing countries

Although translational research is important, its impact may be negligible without a carefully-formulated, broad-based programme to communicate the research to policy-makers. Accordingly, an important component of the DOMI Programme is the synthesis and communication of its research to policy-makers at the international, regional, and national levels. In this regard, the deep involvement of WHO in the DOMI Programme has been crucial since WHO is the leading agency for formulating recommendations about the use of new vaccines in developing countries. Also important have been presentations on DOMI provided to the Global Alliance of Vaccines and Immunization (GAVI). GAVI's partners administer the Vaccine Fund for the purchase of vaccines for the world's poorest countries, and this fund may be critical in the future for the purchase of vaccines against cholera, shigellosis, and typhoid fever for the poor.

DOMI has placed considerable efforts on helping create an adequate and cost-competitive vaccine supply. This has entailed attracting multiple producers to produce targeted vaccines, to enhance competition. DOMI

is working with both international and local producers of oral, killed whole-cell-based cholera vaccine and Vi typhoid vaccine to help create such an environment. For local producers, DOMI is assisting with transfer of production technology and with performance of studies necessary for vaccine licensure. For both international and local producers, the translational research agenda of DOMI, which is generating evidence on disease burden, demand for vaccines, and willingness to pay for vaccines, will serve to provide important information about the potential markets for the vaccines targeted by DOMI.

Involvement of local vaccine producers and a focus on working within the existing research infrastructure of partner countries entails a major commitment to capacity-building. Several, but not all, local producers in the developing world are now capable of producing high-quality vaccines under modern Good Manufacturing Practices conditions. Uptake of new technologies by producers that have not yet reached this level requires technical assistance and training, not only in the production of the new vaccine, but more generically in modern procedures and practices for vaccine production, quality control, and quality assurance. Successful transfer of production technology to local producers may also require technical assistance to their National Regulatory Authorities in the specific activities relating to the new vaccine, and sometimes in more general aspects of modern regulation of biological products. The DOMI Programme has devoted considerable resources to these activities and also works closely with WHO's Global Training Network on Vaccine Production and Regulation. In research, DOMI is providing training to investigators in its partner countries in several areas, including Good Clinical Practices for vaccine trials; computerized data management and analysis; microbiological diagnosis; and the design, conduction, and analysis of sociobehavioural and economic studies relating to vaccine introduction. These capacity-building activities not only help ensure the success of the projects of the DOMI Programme, but also are investments that will assist the partner countries in undertaking programmes of research to generate the evidence needed for rational introduction of future vaccines.

CONCLUSION

That an entire issue of the Journal has been devoted to translational research needed for rational introduction of new vaccines into developing countries underscores

the importance of this emerging, multidisciplinary branch of research. Design of translational research programmes is still in its infancy, as funding for programmes, such as DOMI, has only recently become available. We hope that the papers in this issue will stimulate both thought and debate about the design of research that is needed to inform policy decisions in countries where resources for new vaccines are scarce and where correct decisions are imperative.

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