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Trends affecting the future of vaccine development and delivery: The role of demographics, regulatory science, the anti-vaccine movement, and vaccinomics

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Abstract

Important scientific, cultural, temporal, and secular issues impact the development of, and delivery of vaccines. In this paper we discuss the impact of demographics, regulatory science, the anti-vaccine movement, and finally the impact of the new biology and individualized medicine, which we call vaccinomics, on vaccine development and delivery. A description of the issues and how they have, are, or should be impacting vaccinology is provided, and hopefully will result in increased attention and discussion among vaccinologists. These issues have been under-valued, under-discussed, and in some cases, ignored. We hope that discussion of these issues will result in changes in how we develop, and how we communicate those developments, to the public.

Keywords

Vaccinomics; Vaccine future; Vaccine; Anti-vaccine; Randomized clinical trials; Gene polymorphisms

1. Introduction

In all fields of endeavor it is important to periodically examine temporal, secular, social, economic, scientific, and other trends in order to assess the impact upon the field. With this in mind we explore the effect of four areas we believe will greatly impact the future of vaccinology. These include the role of demographics, regulatory science, the anti-vaccine movement, and vaccinomics. While other issues certainly will impact vaccinology, including issues specific to the developing world, these four issues will have an impact upon the field and may well define vaccinology for the mid- and long-term future. Recognition and cogent discussions of these issues will allow us to prepare for and design the future of vaccine

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Drs. Poland and Jacobson serve as investigators for vaccine clinical studies funded by Wyeth, and an anthrax vaccine trial funded by the CDC. Dr. Poland is the chair of a DMSB for novel experimental vaccines being developed by Merck Research Laboratories. In addition, he has offered consulting advice on vaccine development to GlaxoSmithKline, Novartis, Novavax, Dynavax, CSL Limited and Biotherapies, PowderMed, Avianax, and Emergent Biosolutions. Dr. Jacobson serves on a DSMB funded by Kaiser Permanente concerning HPV vaccine manufactured by Merck Research Laboratories.

development and use, and therefore improve the public health. Certainly wisdom would reside in the ability to try and accurately read these trends and attempt appropriate predictions with a view toward innovation, creativity, and the desire to positively impact the public health. With this in mind, we discuss these issues in the hope that it will allow a "peek" into the future, provoke discussion, and hopefully action, among our colleagues in the field.

2. Demographics

In Western countries all demographic data point to a trend of increasing numbers of elderly persons. Whereas in the 1950s there were an estimated 10 million persons over the age of 65 in the US, by 2020 there will be an estimated 40 million elderly. Similarly in other Western countries, various projections estimate that 30–50% of the population will be age 65 and older by 2040. Recognizing this will have specific consequences and should stimulate specific action on the part of vaccinologists. In particular, a significant investment will need to be made in the science of immunosenescence. Our current understanding of immunosenescence and how to reverse or manipulate it are at best rudimentary. Yet with the aging of the population, the burden of illness due to respiratory and other emerging diseases, the recognition that non-infectious diseases may have immunologic underpinnings that are amenable to immunotherapy, and the increasing health care costs associated with treatment rather than prevention of disease; we must better understand immunosenescence in order to develop vaccines and vaccine strategies that are limited by the aging immune system [1,2].

Such considerations are especially poignant when considering vaccine-preventable disease (VPD) mortality burdens in the US. At the current time, approximately 200 children die of VPDs each year, while 70,000 adults die due to VPD—a stunning 350-fold difference. With further movement of the population structure to older ages, the absolute and relative number of adults ill or dying of VPDs will continue to increase. Thus, improving the immunogenicity and efficacy of vaccines in the elderly, as well as the further development of directed adjuvants to aid immunogenicity, is key to addressing this issue.

3. Regulatory science and vaccine clinical trials

While of incredible value in insuring that only the highest quality (safety and efficacy) vaccines are licensed and approved for use, regulatory science lags behind in innovation. From inception through to licensure, the current process is lengthy, cumbersome, and expensive. With current typical phase III clinical trials now including as many as 40,000 participants, requiring years, and costing tens to hundreds of millions of dollars; vaccine development has become a dangerous and risky financial "gamble". A fall-out effect of this is that vaccine development for licensure will only rest in the hands of very large, multinational companies who can afford the capital outlay for an uncertain financial return. Other fall-out effects will include manufacturers dropping out of the market with products that provide less than optimal capital returns.

As valuable as randomized clinical trials (RCTs) are and hence have become the gold standard by which vaccine efficacy and safety are measured, and hence vaccines licensed, they also have both recognized and unrecognized limitations. For example, RCTs are almost never conducted in all the subpopulations that the vaccine will eventually be utilized in. The hallmark of such trials is extremely restricted inclusion and exclusion criteria and strict "windows" within which vaccines are administered and follow-up provided. This set of criteria almost certainly never reflects "real world" use in the population. It is also possible that important sub-populations might be excluded. For example, it was not until after licensure of the original *Haemophilus influenzae* type b vaccines that it was recognized that native Alaskan and American subpopulations did not respond immunologically as well as other populations that

had been studied [3–5]. Thus, compared to the real world use of the vaccine, many subgroups of interest may be excluded from RCTs.

Finally, RCTs can result in misinterpretation of the data as they only report what happens "*on average*". Often overlooked is that it is quite possible that an individual, as opposed to a group, may benefit from an intervention. So for example, perhaps gene polymorphism "x" leads to a very positive and enhanced immune response to a candidate vaccine. Perhaps this polymorphism has a frequency of 1% in the general population. In an RCT, given the low frequency of the polymorphism and despite its real biologic basis, the value in this subgroup that carry polymorphism "x" would be missed and the candidate vaccine judged poorly immunogenic if it did not induce an immunogenic response in the majority of recipients. No one would advocate eliminating RCTs, but the new science will demand additional clinical study designs that allow detection of smaller subgroup efficacy.

Future developments in regulatory science and study design might require or allow that RCTs be conducted in specific subpopulations (e.g. women, specific ethnic/racial groups, persons carrying a specific gene or genetic haplotype of risk, etc.). Perhaps the need for large RCTs might diminish as other more advanced study designs are developed and tested, or with the development of huge genotype:phenotype databases and the availability of high throughput, low cost genomic sequencing technology. Thus, new tools and resources are needed for vaccine clinical trials.

For example, in phase III clinical trials where the detection of adverse events becomes a key factor in study design, the numbers needed become huge, and hence expensive [6]. The sample size needed in the context of a randomized clinical trial for detecting adverse events rates that vary between events occurring 1 in every 5000 subjects (19,200 subjects needed) to 1 in every 100,000 subjects (384,250 subjects needed) – rates that both patients and physicians care about – are enormous and add considerably to the expense and complexity of conducting clinical trials.

In summary, the current regulatory process is too long, and too expensive. The results may mislead or falsely lull us into misinterpretation because multiple large clinical trials may be needed, the trials do not reflect actual population use, subpopulations are ignored, RCTs have unstated and unrecognized limitations, and finally, there are vastly uneven skill sets within the regulatory agencies themselves. Improvements involving any or all of the components of the regulatory cycle are needed in order to make the process as scientifically rigorous as possible within reasonable and feasible financial realities, and as efficient and timely as possible in order to best impact the public health.

4. Anti-vaccine movement

Numerous papers have documented the negative effects of an anti-vaccine culture on individual and population-level health [7–10]. Numerous examples abound. In the case of measles vaccine, a licensed vaccine used for several decades, unfounded speculations about a possible association with autism and autism spectrum disorder led to detectable population-level decreases in measles vaccine use, in turn leading to a resurgence of measles cases, hospitalizations, and measles-related deaths in the UK [11–13]. In the realm of new vaccine development, the sole manufacturer of a vaccine against Lyme disease eventually withdrew the product from the market due to class-action legal suits [14]. As opposed to parents and individuals with legitimate questions and concerns, the radical anti-vaccine lobby have become "weapons of mass distraction" in trying to educate the public and legislators about the risks and benefits of vaccines.

At least in western culture we have become so risk adverse and risk conscious that the expectation is that no product will ever lead to any harm, under any conditions, in any person —an obviously impossible standard to attain. In addition, the proliferation of Internet sites that post inaccurate and misleading information that unsuspecting parents read and make decisions upon similarly adversely impacts decisions to receive vaccines.

This is reflected in unstated cultural mores that develop over time. In the 1950s, during a time of increasingly mass communication (television, newspapers, radio, etc.) the danger of infectious disease outbreaks such as polio was real and evident. Hence a "good mother" also insured that her children were immunized. The release of the Salk killed-virus polio vaccine in 1955 made the headline of the New York Times and virtually all major newspapers. In today's environment of hyper-mass communication and in the absence of current and immediate infectious disease threats perceived by parents a "good mother" does her homework and starts from the point of concern about vaccine side effects.

The reality is that a growing segment of the public (and of health care workers) mistrusts industry, government, and public health in regards to vaccine safety and efficacy. Stunning examples are evident in this regard. The ministry of health in France temporarily banned the use of hepatitis B vaccines in adolescent females over concerns of an association with demylineating disorders, only to retract it in the face of lack of scientific evidence and a growing incidence of hepatitis B infections among those not immunized [15,16]. Similarly, the use of anthrax vaccine in US military personnel caused considerable controversy and threats of military court martial among troops refusing vaccine over concerns of a myriad of biologically unfeasible side effects [17–19]. Multiple studies all failed to show any association with such side effects. More recently a large multicenter, randomized, placebo-controlled trial of the same anthrax vaccine among civilians failed to demonstrate any significant serious adverse events (interim data available after the first three doses of vaccine) [20].

The reality is that people get vaccines for at least one of three reasons: fear, bandwagoning, or coercion (i.e. the vaccine is required). Bandwagoning deserves some elaboration. Streefland and colleagues have demonstrated that vaccine uptake is heavily dependent upon the sense that those around you, whom you respect, are also taking the vaccine themselves [21]. To the extent that concerns arise, controversy exists and media question safety, etc. this causes people to doubt and by default not receive vaccines. It is the job of HCWs, public health authorities and others to convince the public, using tools and information foreign to how we normally communicate, that recommended vaccines are safe and effective. Otherwise the development of new vaccines against VPD threats means little if vaccine uptake among the public is low. In our opinion, it is unfortunate, but we have moved from evidence-based to media-based medicine, at a cost of excess morbidity and lives lost.

Another trend worth noting is that of media-based, rather than evidence-based consumerism. The consumer-driven, electronic environment we now live in, in conjunction with the proliferation of social networks and the dependence upon the Internet as a source of information results in all ideas being given equal credence, regardless of expertise. This results in information "noise bombardment", a hyper-diversity of ideas and opinions (even when scientifically wrong or naïve), and the result is a scientifically less literate population with a poor risk understanding and risk adverse mindset. For this reason vaccinologists will be familiar with the parent questioning whether it is "safe" for their child to get recommended measles-mumps-rubella (MMR) vaccines, even in the face of a resurgence of measles and mumps in the US that results in hospitalization, permanent harm, and even death.

George Santayana (1923) said that "Those who fail to learn the lessons of history are doomed to repeat them." It appears that in terms of measles, mumps, and rubella outbreaks that he is

right—the public has yet to understand the relationship between population-level uptake of vaccine and the resulting herd immunity and the eradication of vaccine-preventable disease threats; nor the balance of risks and benefits, and the risk of disease resurgence.

5. Vaccinomics and the new biology

We have previously published our view of the coming era of “predictive or individualized” vaccinology, which we refer to as “vaccinomics” [22]. The sciences of biology, immunology, engineering, bioinformatics, genetics, and advanced technology will “change everything” in terms of our ability to direct science toward solving significant infectious diseases and immunology puzzles that slow or prevent vaccine development against threats such as HIV, hepatitis C, malaria, and others. Of concern is that advances in these fields are moving faster than the vaccine world... we are getting “left behind” and unable to adapt rapidly changing technological advances into directed vaccine development. Such technologies must be recognized and harnessed if we are to nimbly address new threats such as bioengineered microbial threats, weaponized viruses, bacteria, toxins, a variety of newly recognized and emerging infectious diseases, and multiply drug resistant pathogens. New technologies such as the use of vaccinomics and mass spectrometry in directed and rational vaccine development will be key. Other examples of technology which can be harnessed toward creating vaccine solutions include transcutaneous immunization, immunostimulant and immunopotentiation strategies, DNA and vectored vaccines, plant production and delivery systems, mucosal immunization, and the development of peptide-based vaccines and directed adjuvants to insure peptide immunogenicity.

Widely acknowledged is that vaccines are among the most cost-effective medical maneuvers we have in medicine. The life span in the US has doubled in the last 100 years due to sanitation and the control of infectious diseases, primarily by vaccines. As a result we attempt to deliver a series of vaccines to every living human on earth but it has been a “one size fits all” approach, or population-level public health approach. In view of the advances in individualized medicine, we need to ask the question “is such an approach informed by the new science”? For example, currently a 1-year-old child and a 40-year-old 120 kg construction worker get the same dose of MMR vaccine. Up to 40% of the adolescent population will respond after 1–2 doses of hepatitis B vaccine—does everyone really need 3 doses? Of HPV vaccine? Who will develop Guillain-Barre Syndrome (GBS) after influenza vaccine? Or neurologic complications after vaccinia or yellow fever vaccine? Such questions cannot currently be answered at the individual level, but with advances in genetic and individualized medicine, may soon be answered.

It is well accepted that drug (therapeutic) effects vary among recipients of drugs and that these are genetically mediated. For example much is now known about the CYP2D6 enzyme and its effect on drug metabolism. Different allelic forms of this enzyme lead to an individual being an ultrarapid, extensive, intermediate, or poor metabolizer of a variety of drugs such as anti-hypertensive, antidepressant, and some chemotherapeutic agents. In a similar manner, polymorphisms in immune response genes can result in variation in immune responses to biologics and vaccines. Defining these polymorphisms offers the chance to determine who is at risk of a serious outcome from a specific infectious disease, the likelihood of a serious adverse event from a vaccine, the number and dose of vaccine needed to induce immunity, and even impact the directed development of new vaccines.

From the 1950s through to today, our approach to vaccine development and delivery has centered on a one “size” fits all approach where everybody is at risk for everything. Current vaccines have been prophylactic only and the development of childhood vaccines has vastly overshadowed vaccines for adults—despite the magnitude of adult morbidity and mortality due to VPDs. In addition, parenteral vaccine development has predominated (except FluMist

and oral typhoid) with no therapeutic vaccines available. In Western countries, only two licensed adjuvants are available, and vaccine development remains empiric in approach. Finally, vaccine development has been almost exclusively within the private, big Pharma sector.

The approach of tomorrow is likely to be a personalized approach which recognizes a tiered risk and vaccination approach, where both prophylactic *and* therapeutic vaccines are available, where the development of adult vaccines exceeds that of vaccines against childhood illnesses, where oral, transcutaneous, depot, and mucosal vaccines utilizing multiple highly specific adjuvants are developed. We will move toward a directed vaccine development approach that better utilizes private and public sectors from industry, public health, and academia.

For those readers interested in more detail, we have recently published comprehensive reviews of vaccinomics and personalized predictive vaccinology [22–24]. In our work, we have demonstrated that viral receptors (e.g. SLAM, CD46), innate receptors (e.g. TLRs), class I and II HLA genes, cytokine and cytokine receptor genes, signaling molecule genes and others have significant associations with variations in immune responses to viral vaccines [25–31]. The point of these studies has been to begin to define associations between important immune response genes and correlate these with variations in immune responses (both humoral- and cell-mediated) to viral vaccines. By understanding polymorphisms and SNPs that are determinative in immune response, it may be possible to either screen for such polymorphisms or to design vaccines that overcome or circumvent such genetic restrictions. Such work evolves from our “immune response network theory” whereby the immune response to a vaccine can be conceptualized as the cumulative result of interactions driven by a host of genes and their interactions, and is theoretically predictable [32]. The basic genetic elements of the network includes genes activating/suppressing immune responses, the dominance profile of a given gene or polymorphism, epigenetic modifications of genes, the influence of signaling genes, innate response genes, gene–gene interactions, and genes for other host response factors.

Similarly, we believe the above efforts should be applied toward vaccine delivery and vaccine safety. We have called this “personalized vaccinology” whereby, in time, we will be able to screen for polymorphisms or other genetic factors that may predict such things as non-response to a vaccine, or a serious adverse event resulting from a vaccine [24]. It may even be possible to screen for disease susceptibility, allowing decisions of whether to offer a vaccine or not.

6. Conclusion

It is our belief that the issues discussed above represent significant factors impacting the future of vaccinology. Understood and addressed, these areas become opportunities to increase immunization rates in populations at risk, particularly in the elderly, decrease health care costs in a scenario of a population structure increasingly of older age individuals, and improve the public health. Each of these issues is foundational in understanding the social, economic, social, and scientific drivers of vaccine development and use within the population. These issues represent some of the “puzzle pieces” in the process from recognition of an infectious disease threat, development of a vaccine, and public use of the vaccine. Despite the best technology available and the development of the best vaccine imaginable, such vaccines are worthless if not used and trusted by the public and health care providers. Public health officials and vaccine developers alike would be wise to engage in a process where such temporal and secular trends are regularly monitored, understood, and addressed.

We also believe that the new biology provides an unprecedented opportunity that will usher in a new golden era of “Predictive and Personalized Vaccinology”. Such an era might allow us to abandon a “one size and dose fits all vaccine approach”, predict whether to give a vaccine

based on likelihood of response, predict the likelihood of a significant adverse event to a vaccine, predict the number of doses likely to be needed to induce a response to a vaccine (HBV and measles examples), and design/develop new vaccines. Such a concept would improve vaccine safety by allowing screening for adverse event susceptibility and improve confidence in vaccines and public health strategy. *In toto*, we believe that the future is both bright and promising for vaccinology as new science and technologic advances continue—particularly in the areas of genetics and immunology. If successful, human health is likely to substantially benefit.

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