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Vaccinology in the third millennium: scientific and social challenges

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The epidemiology of deaths due to vaccine-preventable diseases has been significantly and positively altered through the use of vaccines. Despite this, significant challenges remain in vaccine development and use in the third millennium. Both new (Ebola, Chikungunya, Zika, and West Nile) and re-emerging diseases (measles, mumps, and influenza) require the development of new or next-generation vaccines. The global aging of the population, and accumulating numbers of immunocompromised persons, will require new vaccine and adjuvant development to protect large segments of the population. After vaccine development, significant challenges remain globally in the cost and efficient use and acceptance of vaccines by the public. This article raises issues in these two areas and suggests a way forward that will benefit current and future generations.

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Introduction

The prevention of infectious diseases by the widespread use of vaccines has demonstrably changed the types and incidence of morbidity and mortality due to vaccine-preventable diseases. In fact, the Centers for Disease Control and Prevention (CDC) has ranked vaccines and widespread sanitation as being responsible for the significant decrease in vaccine-preventable disease incidence and deaths [1]. This has been accomplished in two major ways: first, by the development of safe and effective vaccines; and second, by the widespread utilization of these vaccines among the populace. Both these conditions face threats and new challenges in the third millennium. The first challenge is the need to develop new technologies that enable faster and directed vaccine development for hyper-variable and complex disease-causing organisms, and the need for safe and effective adjuvants that can be used to direct and amplify protective immune responses. The second major challenge is the necessity for the populace, as a whole, to voluntarily accept these vaccines as important determinants of their wellbeing and health. In this review, we outline these challenges (see Figure 1) and suggest how they can be met (see Figure 2) in the third millennium.
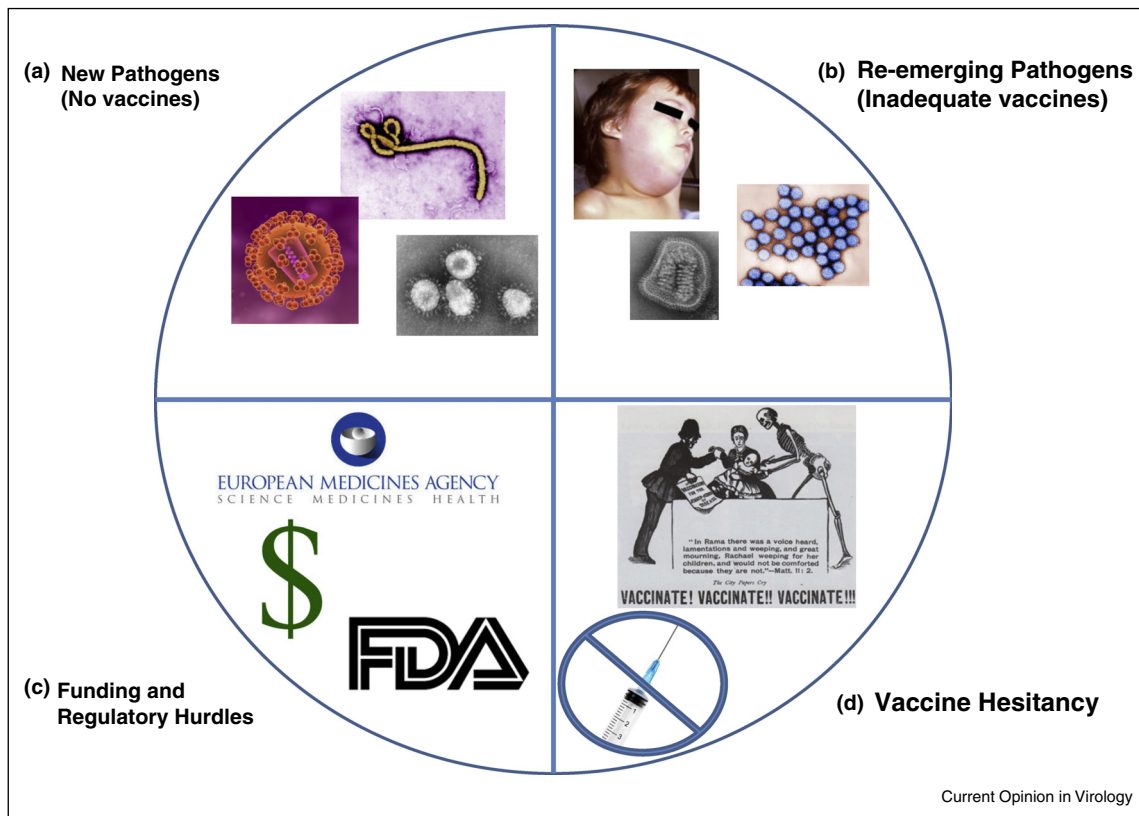
Disease challenges: epidemiology

Despite the immense progress in combating infectious diseases through vaccines, formidable foes remain. HIV, tuberculosis, malaria, and hepatitis C are epidemiologic giants that continue to contribute significantly to global mortality and lack effective vaccines (Table 1). Fortunately, progress has been made on the malaria vaccine front [2]. Some may argue that since we now have highly effective, tolerable treatments for curing hepatitis C, the quest for a hepatitis C vaccine is a moot point; however, the cost and availability of curative therapies is still limited to a select few. HIV and tuberculosis remain the most deadly infectious diseases worldwide [3].

The recent Ebola outbreaks have resulted in 28 639 reported cases with 11 316 deaths as of January 2016 [4] and have raised the spotlight on the need for readily available and effective vaccines against lethal emerging pathogens. Over the past year, significant progress has been rapidly made on vaccines for prevention of Ebola virus disease [5–8]. The design of clinical vaccine trials in the midst of ongoing outbreaks using novel cluster randomized controlled trial designs with ring vaccination is a notable early third-millennium achievement [9]. However, as important as this study design is, would it not have been better if an effective vaccine had already been developed and available?

As the authors of a recent *New England Journal of Medicine* perspective article point out, prior to the Ebola outbreaks

Figure 1

Challenges facing vaccines. **(a)** Pathogens for which we currently lack vaccines (HIV, M. tuberculosis, Ebola, SARS, MERS, among others). These are completely new pathogens that have not been studied, or are more complex pathogens with immunomodulatory traits or hypervariable genomes for which conventional vaccine development approaches have failed. **(b)** Re-emerging pathogens that current vaccines: have been unable to control or eradicate, elicit marginally protective immunity, have unwanted side effects (rotavirus), require multiple booster immunizations (hepatitis B), or require yearly vaccine reformulation (influenza). **(c)** Funding and regulatory issues can be formidable obstacles to the successful research, development, clinical testing, and licensure of new vaccines. These factors may also act as disincentives to even consider vaccine development. **(d)** Anti-vaccination groups are increasingly vocal in their opposition to vaccination. Current communication technologies allow them to rapidly and widely spread their messages against vaccines. As a result safety standards are considerably higher now and public opinion toward a new vaccine must now accurately gauged and considered to an extent never seen before. All images are public domain or are owned by their respective agency/foundation.
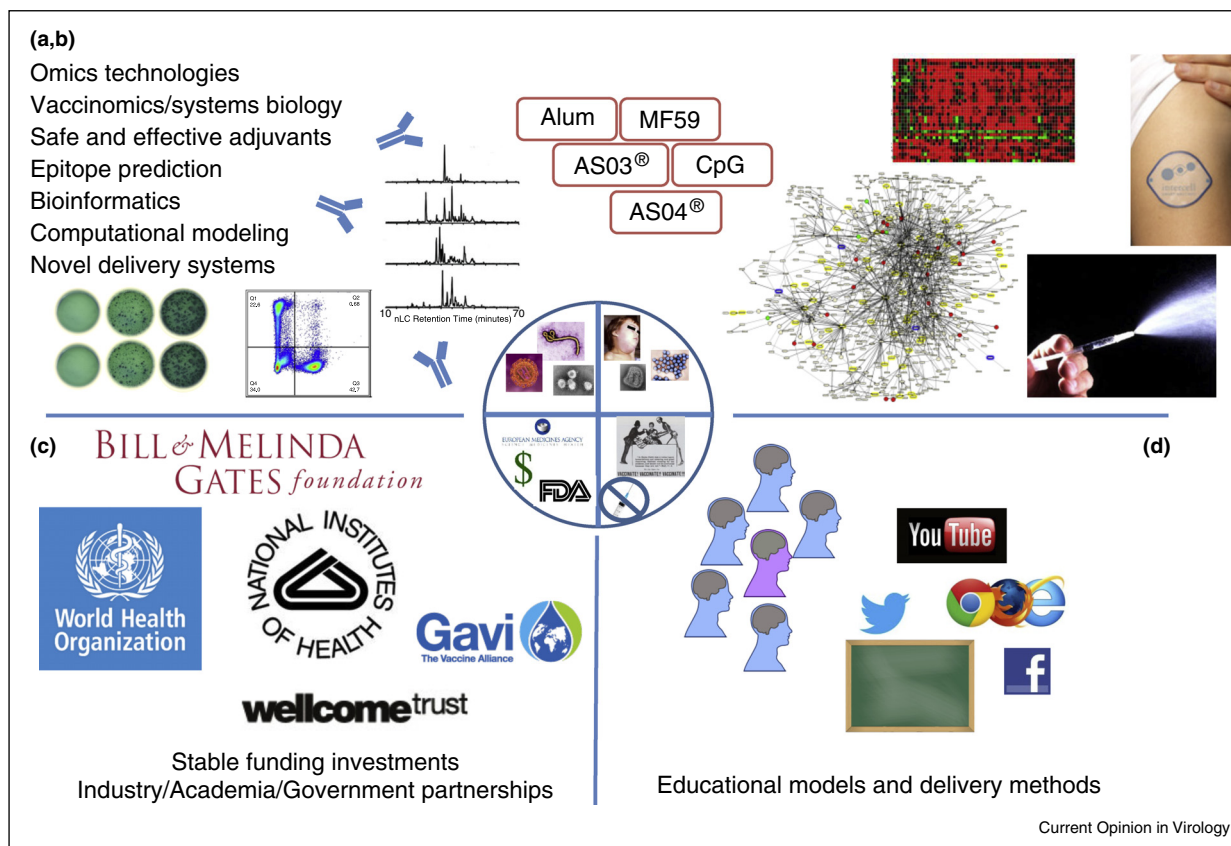
of 2013–2015, at least seven Ebola vaccine candidates had been tested in primates with promising results; however, only one had been tested in healthy humans, and no vaccine had reached later phase clinical trials that would lead to licensure. The authors propose that vaccine development is currently facing a crisis due to several factors: first, the pathogens for which we lack vaccines are complex and require significant investment; second, there are fewer vaccine manufacturers that are able to contribute the required resources for development of new vaccines; and third, the current business model prioritizes the development of vaccines with large market potential [10••]. Vaccine development for other emerging infections (e.g. Middle East respiratory syndrome, or MERS; severe acute respiratory syndrome, or SARS; Chikungunya; West Nile; Dengue; Zika; and Lyme) face these same roadblocks (Table 2).

These challenging pathogens for which we lack promising vaccines, along with the newly emerging pathogens that pose pandemic potential, are not the only reasons we need more vaccine research and development. The pathogens for which we currently have licensed vaccines remain adversaries that continue to challenge vaccine development.

Current vaccine deficiencies

Although remarkably effective, currently licensed vaccines have some limitations. In fact, vaccine failure (i.e. the failure for the recipient to either develop or maintain protective immunity) takes place despite the receipt of a single dose, and/or several doses of vaccines, such as measles-mumps-rubella (MMR), hepatitis A and B [11], influenza [12], varicella [13], Haemophilus influenzae type b (Hib) containing acellular pertussis (DTaP-Hib) [14],

Figure 2

Solutions to the current vaccinology problems. **(a and b)** Cutting edge technologies allow investigators to study the immune system with unprecedented detail and scope. These technologies, along with novel analytical routines designed to handle the massive datasets, will provide greater insights into immune function and vaccine response. Studies targeting adjuvants and innate immune pathways will also be incorporated into the design of more effective vaccines, perhaps involving novel delivery systems such as the intradermal or intranasal routes pictured. (b) International partnerships that bring together scientific leaders from academia, product development expertise from industry, public health officials, and funding/support from private foundations and governmental agencies will be necessary to provide the stable, long-term support and resources necessary to create safe and effective vaccines. **(c)** Coordinated educational efforts that encompass multiple traditional and novel communication platforms will allow widespread delivery of scientific knowledge and data-driven findings. Physicians, healthcare providers, and patients will have open dialogs that acknowledge concerns and provide information tailored to the patient's preferred learning styles.

and other vaccines. Antigenic changes in influenza viruses require us to reformulate and administer the vaccines every year. We and others have demonstrated that host genetics (SNPs in HLA and other immune response genes) and other host factors may play a significant role in variations in adaptive immune response to vaccination, including vaccine failure [15••,16–19].

However, there are some limitations with vaccines containing live attenuated (MMR, varicella, smallpox, zoster, and yellow fever) or killed whole/inactivated (polio, influenza, Hepatitis A) microbial organisms, antigenic subunits of these pathogens (pertussis, pneumococcus, and anthrax), or genetically engineered (hepatitis B, cholera, and HPV) vaccines. The main deficits in these vaccines are the requirement for a cold chain, the induction of low seroconversion rates in some subpopulations, interference from

pre-existing maternal antibodies, the requirement for multiple doses, and, for vaccines containing live organisms, the inability to use the vaccine in immunocompromised individuals. Recently, there has also been a resurgence in pertussis (whooping cough) incidence in many countries around the world with many cases occurring in previously vaccinated children and adolescents [20•,21].

New viral vaccine candidates have recently been introduced for varicella-zoster, influenza, dengue and other viruses; however, much remains to be done. For example, the short-term efficacy of the live virus herpes zoster vaccine was demonstrated to be 69.8% in a randomized study of over 22 500 vaccine recipients [22]. Zoster vaccine efficacy was shown to decrease with increasing age at vaccination [23]. An AS01-adjuvanted varicella-zoster virus glycoprotein E (gE) subunit vaccine has undergone clinical

Table 1

Major global infectious disease challenges that lack effective vaccines

Pathogen/disease	Global morbidity and mortality	Vaccine challenge
HIV	37 million people worldwide living with HIV end of 2014; 1.2 million deaths due to HIV in 2014 [100]	Highly variable virus; unclear immune correlates of protection
Tuberculosis	9.6 million new cases of tuberculosis active infection and 1.5 million deaths in 2014 [101]	Unclear immune correlates of protection; 1/3 of world's population infected with latent tuberculosis
Malaria	214 million cases of malaria and 438 000 deaths in 2015 [102]	Antigenic variation during stages of infection; complex host-parasite interaction; unclear immune correlates of protection
Hepatitis C (HCV)	130–150 million people are infected; 500 000 deaths occur each year due to HCV-related liver disease [103]	Genetic diversity among viral strains; hypervariable virus; unclear immune correlates of protection
Dengue	390 million infections may occur each year, of which 96 million manifest clinically [104]	Four virus serotypes; lack of adequate animal disease model; incomplete understanding of immune correlates of protection

trials where it demonstrated acceptable safety and enhanced immunogenicity; the vaccine is under review by the FDA with likely approval in 2017 [24,25]. The world's first tetravalent dengue vaccine has been recently approved for the prevention of dengue infection that is caused by all four dengue virus serotypes in children and adults 9–45 years of age [26]. Two seasonal influenza vaccines, the MF59-adjuvanted influenza vaccine and the high-dose influenza vaccine, are now licensed for use in older adults (≥65 years of age). It has been shown that the MF59 adjuvant increases humoral immune response to various influenza strains, including cross-reactive strains [27,28]. A large influenza vaccine study in 7082 individuals demonstrated significantly higher immunogenicity of MF59-adjuvanted vaccine compared to a conventional non-adjuvanted influenza vaccine for both homologous and heterologous influenza A strains [29]. The immunogenicity and efficacy of high-dose influenza vaccine (60 μg hemagglutinin per strain), compared to standard-dose vaccine (15 μg hemagglutinin per strain), was assessed in a large vaccine study in 31 989 older individuals, which demonstrated the higher immunogenicity of high-dose influenza vaccine compared to conventional vaccine and the improved protection against influenza [30]. However, there is some evidence that AS03 adjuvants used in pandemic influenza vaccines may be associated with the development of autoimmune and neurological disorders like narcolepsy [31]. Thus, we

need a better understanding of determinants of vaccine immunogenicity — both markers that correlate with protection (innate and adaptive antibody and T-cell-mediated cellular) and those that control vaccine failure [32].

As another example, rates of primary (i.e. lack of antibody following vaccination) and secondary (i.e. waning or inadequate antibody following vaccination) measles vaccine failure are projected to be 2–10% and <0.25%, respectively [33,34]. Similarly, after three or more doses of hepatitis B vaccine, 5–10% of persons fail to mount protective titers (≥10 mIU/ml) of hepatitis B surface antigen antibodies [35,36]. Furthermore, the current inactivated influenza vaccine is deficient in its ability to mount an effective immune response in many aging and older individuals. In fact, on average it protects only 30–40% of adults ≥65 years old versus 70–90% of younger adults from contracting influenza viral infection [37].

Although vaccines are one of the most effective public health means for preventing disease and death, they are not perfect and can cause side effects, unforeseen reactions, or vaccine adverse events (AEs). Fortunately, most reactions associated with vaccines, such as redness, soreness, swelling, rash or fever, are mild and transient. Serious AEs after vaccination are uncommon, but they may involve Guillain–Barré syndrome (after swine flu

Table 2

Emerging and reemerging viral pathogens

Virus/disease	Case frequency	Main geographic distribution
Ebola	2013–2015 outbreaks: 28 639 cases and 11 316 deaths [105]	Central and West Africa
Marburg	Sporadic outbreaks; largest was in Angola in 2004 with 252 cases [106]	Central Africa
Lassa Fever	100 000–300 000 cases/year [107]	West Africa
SARS	8098 cases during 2003 outbreak [108]	Southeast Asia
MERS-CoV	1638 cases since 2012 [109]	Arabian peninsula
Chikungunya	>1.3 million cases as of April 2015 in the Americas [110]	Africa, Southeast Asia, Americas
Zika	Not available [111]	South/Central America since May, 2015 (previously Africa, Asia)

SARS = severe acute respiratory syndrome; MERS-CoV = Middle East respiratory syndrome coronavirus.

vaccine, under one case per 100 000 vaccinated) [38–40], narcolepsy (following a AS03-adjuvanted influenza vaccine, one case per ~16 000 vaccinated) [41,42], severe rash and allergic reaction (after influenza, MMR and yellow fever vaccines, one case per ~100 000) [43–45], seizures and acute encephalopathy (after whole-cell pertussis vaccine, the estimated risk is 6–9 cases per 100 000 vaccinated) [46,47], and paralytic polio (after live attenuated oral polio vaccine, 1 case per 2–3 million vaccinated) [48]. Clinical and laboratory research is critical for determining the causal mechanisms of such AEs. Rapid advances in the field of 'adversomics,' which our group defined as being 'the application of immunogenomics and systems biology to understand the genetic and non-genetic drivers of vaccine AEs at the molecular level,' are informing the development of new vaccines [49,50••].

The ultimate goal of vaccine research is to develop better vaccines and new adjuvants against major infectious diseases, including safe and effective vaccines for tuberculosis, rotavirus, malaria, HIV and other emerging and reemerging pathogens. Advancements in healthcare have contributed to the aging of the global population and the growing number of persons with immunocompromising medical conditions. Along the same lines, the population of many developed nations is aging rapidly and so the impact of immunosenescence, or the age-related decline in immune function, must be considered. This is especially important for diseases, such as influenza, with a disproportionate public health impact on older individuals. Additional vaccine strategies are needed to overcome the immunosenescence and immunodeficiencies of these populations. Further efforts are also needed to better understand age-related and gender-related changes and defects in the regulation and function of innate and adaptive immune responses to vaccines. This will be essential to the development of vaccines or treatments that overcome immunosenescence [51–53].

Acceptance of vaccines

The continued, widespread acceptance of vaccines remains a critical component to the overall effectiveness of those vaccines in maintaining individual and herd immunity, and therefore public health strategy. While a large percentage of the population still readily accepts vaccines as safe and reliable, a growing subset of the population believes that vaccines are unsafe or potentially even deadly. Generally speaking, this subset believes that vaccines have a higher potential to be dangerous than actually contracting the disease, leading them to make choices against vaccination. Therefore, it is critical that those in the healthcare profession are able to help individuals choose to accept vaccines. However, numerous issues and determinants play out to create hesitancy or refusal to accept vaccines.

In an article by Poland and Bronson [54•], the authors discussed the importance of examining the layers of closely linked factors (proximate determinants) and external factors (non-proximate determinants) affecting vaccine decision making in order to address vaccine acceptance or hesitancy. This critical, and often overlooked, point was summarized by saying:

"The reality of childhood vaccination uptake...is much more complex. Proximate determinants don't exist in vacuums. They can and do interact with each other and they can vary from person to person, from group to group and over time in complex, non-intuitive ways. Additionally, non-proximate determinants can also affect how vaccine uptake plays out for both individuals and groups. Psychological, ethical, social, cultural, political, economic, ecological and historical factors, not to mention interpersonal, institutional and state power structures can also influence whether or not children receive vaccines [54•]."

In the third millennium, people are now more 'connected' than ever before due to ease in global travel, the increase in technology availability and internet access, and the globalization of our society; this in turn complicates the issue of vaccine hesitancy or acceptance. As humans don't exist in a vacuum, neither do the decisions they make. In this millennium, it is critical to address these issues by understanding the various lenses through which individuals make decisions: their personal beliefs, their individual preferred cognitive styles, and the proximate and non-proximate determinants that impact their lives.

In a recent editorial, two of us (CMP, GAP) [55] outlined six preferred cognitive styles an individual may employ in decision making regarding one's health. A cognitive style is simply a preferred way of thinking that helps an individual understand and process the world. When healthcare workers (HCWs) seek to understand an individual's preferred cognitive style and communicate with them based on that style, they can help address vaccine hesitancy in a way that the patient best understands. As a result, the patient may choose to engage in healthy behaviors and choices. The task of processing vaccine hesitancy or rejection with a patient is extremely important, and to do so in such a way that the patient has the best chance of making a wise decision. The Preferred Cognitive Styles and Decision-Making model emphasizes that medicine is increasingly moving to a more individualized style of care, and using a patient's preferred cognitive style (thus employing psychology and mental health within the medical office) allows patients to engage with an even more personalized style of care, while increasing the probability that through health education patients make better informed vaccine decisions [54•,55,56].

New vaccine development

As described in the previous sections, new vaccine products have multiple obstacles to overcome: first, the

current set of pathogens for which we desperately need new vaccines are considerably more complex than previous vaccine targets; second, empirical approaches to vaccine development (Isolate, Inactivate, and Inject) do not work for current pathogens; third, regulatory hurdles are greater now than they have been in the past; and fourth, an increasingly risk-averse culture demands significantly higher safety standards for vaccines. These challenges are counterbalanced by the tremendous advances that have been made in the fields of immunology and vaccinology that provide exciting tools to overcome these challenges.

Despite the phenomenal success of early vaccines, we still do not fully understand, at a mechanistic level, the rules governing immunogenicity and the development of protective immunity. A collective endeavor to address this knowledge gap, entitled the 'Human Vaccine Project,' [57**] is bringing together researchers, academic institutions, public health agencies, industry, philanthropic foundations, and non-governmental agencies to define the underlying rules of immunogenicity in order to develop safer and more effective vaccines [58,59].

We have learned an incredible amount about the immune system in the last decade, including the characterization of new T helper subsets, regulatory T cells, dendritic cells, and macrophages; [60–64] the recognition of the role of the microbiome and innate immunity in the development and maintenance of robust adaptive immunity [65•]; the development and use of novel adjuvants [66,67]; and a growing body of research aimed at developing a comprehensive understanding the immune response as an interconnected, networked, complex system [68••,69,70••].

Advances in the tools, technologies, and research reagents available for the study of biological systems have also seen recent dramatic changes (Table 3). Next-generation sequencing technologies now allow investigators to rapidly sequence pathogen genomes, conduct global gene expression studies with increased sensitivity, identify rare mRNA transcripts, and alternate splicing, conduct genome-wide DNA methylation analysis, perform ChIP-Seq, and numerous other applications [71]. These technologies are now being adapted to the study of single cells [72]. Advances in multiparameter flow cytometry and the integration of mass spectrometry (CyTOF) enable researchers to simultaneously study 40+ parameters of cellular phenotype and function at an individual cell basis [73–75]. Cutting-edge bioinformatics algorithms and routines capable of handling 'Big Data' are providing sophisticated methodologies to integrate, visualize, and interpret these datasets [76–78,79•,80].

We have coined the term 'Vaccinomics' for systems biology approaches that include immunogenetics and immunogenomics to studying immune responses to vaccines, and applying this knowledge to directed vaccine development. Similar approaches such as 'Systems Vaccinology' or 'Computational Immunology' [32,68••,70••, 81–88,89••,90,91] have also been coined. Vaccinomics is a collaborative approach that brings together biology, computer science, statistics, and bioinformatics. Together, these multidisciplinary teams perturb the immune system in carefully controlled ways and collect high-dimensional datasets characterizing the immune response at multiple levels (the transcriptome, the epigenome, the proteome, the metabolome, the lipidome — including individual molecules, cell populations and surface/functional phenotypes, and tissues/organs). The data is then

Table 3

New technologies for vaccine research.

Technology or tool	Description
Next generation sequencing	Massively parallel sequencing platforms that generate millions of bases of sequence reads in a relatively short timeframe. These platforms have a wide variety of applications including, but not limited to: whole genome sequencing, transcriptome profiling, or identification of genome-wide patterns of miRNA patterns or DNA methylation.
Proteomics	Mass spectrometry techniques for the unbiased, semi-quantitative characterization of the entire protein content of a sample.
CyTOF	Mass cytometry. Single cell analysis platform combining mass spectrometry with flow cytometry. Antibodies are tagged with heavy metal ions and used to stain cell populations of interest. Spectral overlap limits flow cytometry to ∼20 markers. CyTOF has increased signal resolution and potentially offers 10× as many parameters.
Vaccinomics/Systems biology	An approach to understanding variations in immune response to vaccines that utilizes high-dimensional technologies to fully characterize, at an omics level, the perturbations elicited by vaccination. This rich dataset is then analyzed using bioinformatic tools and computational modeling to create a predictive model of immune responses that can be tested and improved through iterative experimental cycles.
Single cell sequencing	A set of methods for capturing the transcriptome of individual cells. Methods include: STRT, SMART-Seq, Quartz-Seq, and CEL-Seq.
Epitope prediction algorithms	A set of computational tools that use binding motif databases, artificial neural networks, hidden Markov models, support vector machines or other methods to predict MHC-binding peptides in protein sequences. Examples include: SYFPEITHI, BIMAS, PREDEP, and RANKPEP.

organized, integrated, and mined using sophisticated computer algorithms and bioinformatics approaches in order to develop predictive and/or mechanistic models of immune function [76]. These models are then tested in a new round of experimentation that, in turn, yields additional insights and raises more biological questions.

We believe that this work will be crucial toward understanding the complex interplay between human beings and the pathogens of high public health interest [92]. These types of studies will allow a rationale, logical, and directed approach to developing novel vaccines and improving current ones.

More effective vaccines are also needed for certain population groups. Successful vaccination of older individuals is often complicated by pre-existing medical conditions and medicine usage. Similarly, infants and young children have immune systems that have not yet fully developed and respond to infection/vaccination differently than adults [93,94]. The development of more effective vaccines and treatment options for the very young and for older individuals will require a more comprehensive understanding of how the various components of the immune response collectively respond to immunization or infection [95,96•,97–99]. Vaccinomics approaches integrating high-dimensional datasets and predictive modeling will likely play a central role in these efforts.

The way forward

The above brief review highlights the challenges facing the field of vaccinology in the third millennium. There are a few 'foundational pillars' around which teams of scientists must collaborate: issues of emerging diseases that threaten health of humans and animals; the need for novel vaccine adjuvants; the challenges of vaccine research and development financing; and the science that is developing around the critical need to communicate, educate — and convince — the populace to endorse and accept vaccines.

We also call attention to the growing need for bioinformatics in 21st century vaccine development. Currently, however, few bioinformaticians are involved in vaccine research; given the early growth of the field, the tools and analytic routines needed for assisting new vaccine development are at an early stage of development. Such tools are needed if we are to take advantage of the economies of 'big data' [76].

To the above mix, it is apparent that the costs associated with new vaccine development continue to increase, often requiring $1 billion to get to licensure. This, in turn, requires stable and sustained investment, and a more seamless integration of vaccine financing from basic research, to preclinical development, to clinical development, to population utilization. Currently, this route is

expensive, fragmented, discordant, disconnected, and uncertain. This state of affairs leads to more expense, delays in bringing new vaccine candidates into clinical trials, and results in continuing unmet public health needs. A recent editorial reviewed some of these issues and suggested the development of a global vaccine development fund [10••]. We find this novel concept to be compelling, as it is highly likely to galvanize the necessary teams of scientists and financial and regulatory infrastructure needed in order to make achievable progress and meet the needs of a diverse and changing global public health need.

Conflict of interest

Dr. Poland is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland offers consultative advice on vaccine development to Merck & Co. Inc., CSL Biotherapies, Avianax, Dynavax, Novartis Vaccines and Therapeutics, Emergent Biosolutions, Adjuvance, and Microdermis. Drs. Poland and Ovsyannikova hold two patents related to vaccinia and measles peptide research. JA Whitaker receives funding for Mayo Clinic research from Pfizer Independent Grants for Learning and Change. RB Kennedy is funded by Merck Research Laboratories to study waning immunity to mumps. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and was conducted in compliance with Mayo Clinic Conflict of Interest policies.

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