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Addressing viral resistance through vaccines

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Abstract

Antimicrobial resistance is a serious healthcare concern affecting millions of people around the world. Antiviral resistance has been viewed as a lesser threat than antibiotic resistance, but it is important to consider approaches to address this growing issue. While vaccination is a logical strategy, and has been shown to be successful many times over, next generation viral vaccines with a specific goal of curbing antiviral resistance will need to clear several hurdles including vaccine design, evaluation and implementation. This article suggests that a new model of vaccination may need to be considered: rather than focusing on public health, this model would primarily target sectors of the population who are at high risk for complications from certain infections.

Keywords

antimicrobial resistance; antiviral resistance; cytomegalovirus; hepatitis C; HIV; influenza; vaccines; vaccine design; vaccine evaluation; vaccine implementation

The impact of antibiotic resistance on the fabric of healthcare has stirred significant concerns, debates and interest regarding the future of treatment for bacterial pathogens. The facts are clearly alarming. In the USA alone, more than two million people a year become ill through infection with bacteria for which the normal course of antibiotic treatment has little effect. Of those, approximately 23,000 people die due to the lack of an appropriate antibiotic to treat their infections [1]. Antibiotic stewardship, including the improper use of antibiotics for viral infections, dearth of new drugs in the pipeline, lack of industry investment in new antibiotic research and development, and prophylactic antibiotic usage in animals are cited as factors that contribute to this emerging threat. On the other hand, antiviral resistance is rarely mentioned or considered as a possible issue of concern. The reason for this inattention is primarily timing. Early success with the development and use of vaccines for many childhood viral infections such as polio, measles, mumps and rubella removed much of the urgency for antiviral development. Antibiotic development, however, became a thriving industry in the early to mid-twentieth century. Bacterial targets were easily identifiable and

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had the added benefit of being broad spectrum, or effective across a range of bacterial pathogens. When coupled with the relative ease of identifying bacteria as the source of an infection through low cost diagnostics and symptomatology, the use of antibiotics became routine and even excessive. Resistance was observed, but this was balanced by the discovery of alternative antibiotics and the relative ease of modifying existing antibiotic classes with high success rates. However, a disruption of the treatment equipoise soon ensued as the ability to discover and supply new antibiotics was overtaken by the emergence of resistance. It was only with this disruption that the issue developed into a potential crisis requiring immediate attention.

The timing of the emergence of drug resistance also relates to the significant differences between antibacterials and antivirals. Most bacteria are free living, so drugs generally target properties that are shared among many bacterial families but not found in their hosts. Consequently, antibacterials are often broad spectrum and have minimal toxicity. In contrast, viruses are obligate intracellular parasites that rely on host cellular functions to replicate. Thus, most currently available antivirals target specific viral functions and many have significant toxicities. The means of transmission of resistance differs as well. Although both bacteria and viruses transmit genes vertically to their progeny, some bacteria can also transmit genetic information horizontally, which greatly increases the spread of resistance. In the early 1980s, the dwindling of the antibacterial pipeline and the increasing awareness of the consequences of overuse coincided with the growth of interest in antivirals, spurred heavily by the need to immediately address the growing HIV/AIDS epidemic [2]. The advent of HIV stimulated an explosive level of discovery and validation of antiviral efficacy that led to the search for therapies for many other viral infections. The HIV efforts also birthed the concept of treatment with combination classes of antivirals, resistance monitoring and compliance education using a select cadre of health care workers highly trained in the treatment and care of HIV-infected individuals. This resulted in a new approach to the use and stewardship of antimicrobials [3].

As of late 2014, there were approximately 30 individual direct-acting antiviral drugs approved for the treatment of HIV, as well as several combination drugs [4]. In addition, there were just over a dozen direct-acting drugs in common use for six other viral infections (HBV, HCV, influenza, HSV, varicella zoster virus [VZV] and CMV). Unsurprisingly, the development of antiviral resistance promptly followed the introduction of these drugs, to a greater or lesser extent. There are now only a few approved antivirals, such as ribavirin and imiquimod, which target cellular functions and are not associated with resistance. Of note, there are approved vaccines for four of the nine viruses that have antiviral therapies (HBV, influenza, HPV and VZV), and for nine others viruses that do not have approved antiviral therapies [5] (see Table 1 for more information on available vaccines and antivirals along with associated resistance [6–8]).

Definition of the issue: antiviral resistance

Several features of infection can influence the probability of the appearance of antiviral resistance. The primary one is the fidelity of genome replication. Viral polymerases of double-stranded DNA viruses have a high degree of fidelity as there is a complementary

second strand to verify the correct sequence. Most also have an exonuclease activity that can excise any incorrectly selected nucleotides. On the other hand, viruses with single-stranded RNA genomes often have error prone polymerases and routinely make approximately one (range: 0.1–10) incorrect base selection during each round of replication [9]. Influenza is an excellent example in which an error-prone polymerase results in the rapid emergence of viruses resistant to both classes of antiviral therapies, the adamantanes and the neuraminidase inhibitors. For some viruses, a contributing factor is the long duration of viral replication seen in chronic infections such as hepatitis B and C, which increases the opportunity for errors during replication. Finally, the immune status of the host can also be important. Mutations that confer resistance often develop in immunocompromised individuals whose immune systems do not effectively clear infections and thus allow multiple rounds of viral replication and consequently more opportunities for errors. Hematopoietic stem cell and solid organ transplant recipients, as well as HIV-infected individuals, are classic examples of this phenomenon.

HIV and influenza provide examples of two RNA infections, one chronic and one acute, for which resistance is a serious clinical concern. HIV is a retrovirus with nine genes on a single RNA genome that replicates through a process of reverse transcription into a DNA template. The virus replicates rapidly, making as many as a billion new viral particles each day, which leads to high mutation rates. Like RNA genome replication, reverse transcription is an error-prone process and often results in the generation of drug-resistant mutants. Further increasing the mutation rate is the ability of different strains of HIV to recombine to produce additional variants, such that many strains of HIV can be present in a person at once [10]. As opposed to curing the infection, available HIV treatments are only able to suppress the amount of virus in the body. There are six major classes of HIV drugs, which are characterized by how they interfere with the virus' replication cycle. With very few exceptions, they are direct-acting antivirals that target a viral function and are susceptible to the development of resistance. Consequently, a combination of antiretroviral drugs that individually target at least two different viral functions has become the standard approach toward treatment. According to the WHO, two million HIV-infected people started antiretroviral therapy (ART) in 2013 – the largest ever annual increase [11]. For a disease that affects approximately 35 million people worldwide, this is a major milestone [12]. However, the steady improvement in availability and distribution of ART has also led to an increase in drug resistance. A WHO-conducted literature review showed that the prevalence of transmitted drug resistance in select low- and middle-income countries increased between 2003 and 2010 and peaked in 2009 with a rate of 6.6%. In terms of transmitted drug resistance, WHO surveys found that the prevalence among people starting ART increased from 4.8% in 2007 to 6.8% in 2010 [13]. Because antiretrovirals have been available in the USA for a longer period of time, drug resistance is subsequently a larger problem. It is estimated that 15% of newly diagnosed HIV infections in the USA carry mutations associated with transmitted drug resistance [14]. The prevalence is concerning and may become a larger issue as ART becomes more readily available worldwide. Additionally, while there have been major improvements in effectiveness, these medications are not without side effects. Significant long-term side effects of HIV treatment include insulin resistance, lipid abnormalities and decreases in bone density [4]. These issues can cause

patients to deviate from their prescribed treatment regimen, allowing the virus to replicate more and increasing the potential for mutations to develop.

Influenza is another example of an infection whose treatment is characterized by the rapid emergence of antiviral resistance. Its genome is single-stranded RNA and composed of eight segments. Similarly to HIV, influenza drug resistance arises as a result of several factors, including an error-prone viral RNA polymerase, many rounds of replication in an infected person and the occurrence of reassortants among the different genomic segments. The adamantanes were the initial approved antiviral therapies for flu and they worked by inhibition of the M2 viral protein that establishes ion channels necessary for viral uncoating. Global resistance levels were 12.3% in the 2003–2004 season and this rose to 92% in the USA in the 2005–2006 season [15]. Consequently, these drugs are no longer recommended for either therapy or prophylaxis of flu.

The adamantanes were supplanted by a new class of influenza inhibitors, which act at the level of the viral neuraminidase. The neuraminidase inhibitors, primarily zanamivir and oseltamivir, are analogs of sialic acid, which is the neuraminidase substrate. They prevent the release of progeny viruses. Unlike the adamantanes, they are active against both influenza A and B and they can also be used for prophylaxis. Significant levels of virus resistant to the neuraminidase inhibitors began to emerge in the 2007–2008 season and the level of resistant virus was essentially 100% by 2009. The finding that resistant virus dominated in many geographic areas where oseltamivir had not been used suggests that it may have had a fitness advantage over the parental virus strain [16].

Control strategies

As evidenced by the examples of HIV and influenza, strategies are needed both to control the effects of antiviral resistance in an infected population/individual and to limit its emergence and transmission. The approach that has been used the most is to treat patients with a combination of two or more drugs with different mechanisms of action rather than with a monotherapy. This approach has been successful in preserving treatment regimens for HIV infection as well as for HCV and HBV infections. The concept is simple. It is predicted that if resistance emerges to one therapy, the other drug will eliminate the mutant, and a newly emergent double mutant is extraordinarily unlikely. An additional potential advantage of combination therapy is that it may result in additive or even synergistic levels of antiviral activity. A potential downside is that the toxicities may also be increased.

However, as witnessed with the emergence of HIV resistance, this system is imperfect. Mutants do arise, albeit at rates much lower than would have been predicted with monotherapy. Another potential disadvantage is the cost. The newly approved sofosbuvir, an HCV RNA polymerase inhibitor, can cost as much as US\$84,000 for a 12-week course [17]. That price increases when sofosbuvir is combined with the newly approved HCV protease inhibitor, simeprevir. While this is a one-time cost since the treatment clears this chronic infection, it must be stressed that this cost is well beyond the means of most people in the world and the control of HCV will almost certainly require the development of an effective vaccine. As discussed, HIV treatment is not curative but instead turns a deadly infection into

a chronic one. The annual treatment cost per HIV patient in the USA was estimated to be US \$23,000 in 2010 [18]. While exact costs depend on several variables, it is clear that treatment costs can be prohibitive. Another potential drawback is that combination therapy requires the availability of two compounds that act by different mechanisms. Although there are several therapies approved for both HSV and VZV, they largely all have the same target, the viral thymidine kinase. For CMV, there are two approved drugs with different targets, valganciclovir (UL97 kinase inhibitor) and cidofovir (viral DNA polymerase). However, they each have serious toxicities and cannot be used in combination. For influenza, a current research emphasis is to identify new agents that target something other than the viral neuraminidase. Two drugs currently in clinical trials reflect this strategy. Favipiravir targets the viral RNA polymerase and might be combined with a neuraminidase inhibitor. Indeed, *in vitro* data show that favipiravir has synergistic activity when combined with oseltamivir against an oseltamivir-sensitive pandemic influenza A H1N1 strain, and additive activity against a comparable resistant strain [19]. DAS181, another candidate for monotherapy, targets the host sialic acid, the influenza receptor. This drug would be unlikely to induce resistance and could also be used in combination. However, it is clear that, because of the potential emergence of resistance, antivirals alone cannot be relied upon to provide adequate protection against these infections.

Another recent strategy to combat antiviral resistance is the development of broad-spectrum antivirals that target host, rather than viral, functions. These take advantage of the viral need for functions provided by the host for replication, and thus act indirectly. It is assumed that essential host functions cannot become resistant without harming the host. These antivirals have an obvious potential for unacceptable toxicity. However, viral replication sometimes requires more of a particular function than the host does. It is sometimes possible to define a therapeutic window of dose concentrations that will inhibit the virus and not seriously harm the host, as there may be some salvage pathways that the host, but not the virus, can use to supply the inhibited function.

The most relevant strategy for this discussion is the use of vaccines as a means to limit the impact of antiviral resistance. When the majority of a population receives prophylactic vaccination, the incidence of an infection sharply declines with the reduction in number of susceptible individuals. This has been demonstrated repeatedly as shown in Figure 1 [20–27]. As a corollary, the opportunity for the emergence and potential transmission of resistant viruses also sharply decreases. At the individual level, vaccination is rarely sterilizing. A protective vaccine may still allow a few rounds of viral replication before controlling the infection. However, the reduced number of rounds of viral replication in the vaccinated, infected individual greatly reduces the opportunity for replication errors, the emergence of resistant progeny and the further transmission potential within the broader and preferably well-immunized population. In some cases, vaccination can be given as pre-exposure prophylaxis to a limited number of people in response to an outbreak. One form of this strategy, known as ring vaccination, consists of identifying and vaccinating contacts of a sick individual in the hope of quickly preventing spread. This was used in the eradication of smallpox and is now being used in a trial of an Ebola vaccine in West Africa [28].

New directions: the challenges in vaccine research

To reach the goal of controlling antiviral resistance through vaccines, we first need to invest in research, development and implementation approaches for those high priority viral infections associated with the emergence of drug resistance. It is generally agreed that most of the straightforward vaccines have been developed and that multiple challenges remain for the design and evaluation of our next generation vaccines. Some of the issues most relevant to vaccines primarily focused on addressing antiviral resistance include the following:

Design

As discussed above, the standard approaches to vaccine design have worked well for many viruses, but vaccines for other viruses remain elusive despite the expenditure of extensive efforts. One of the main obstacles probably lies in the current inability to design an optimal immunogen. This is certainly the case for viruses such as HIV, HCV and influenza whose replication involves a high variability and mutation rate. Initial strategies to develop an HIV vaccine focused on the envelope protein, gp120. However, these candidate vaccines often did not neutralize clinical isolates, which contain many variants. Fortunately, new advancements in structure-based vaccine design may help solve this problem. These newer strategies exploit broadly neutralizing antibodies and knowledge of the structure of the antigenic epitope to guide the design of improved immunogens [29,30]. The structure of a peptide or protein in complex with a broadly neutralizing antibody serves as the starting point for design of 'epitope-scaffold immunogens,' in which continuous or discontinuous epitopes are transplanted via various grafting methods to unrelated scaffold proteins for epitope conformational stabilization and immune presentation [31–35]. To improve on the original epitope scaffold approaches that were limited to scaffold proteins of predetermined structure, Correia *et al.* recently developed a novel computational method (i.e., Fold From Loops) that allowed the design of scaffold proteins with full backbone flexibility. Using an epitope from respiratory syncytial virus (RSV), they demonstrated that this new method resulted in epitope scaffold immunogens that more accurately mimicked the viral epitope structure, and thus induced not only structurally specific antibodies, but also potent neutralizing antibodies [36]. The ultimate goal and rationale of structure-based vaccine design is to generate a vaccine that provides broad coverage against multiple strain variants of a given pathogen. Such an accomplishment was achieved for *Neisseria meningitidis* (MenB) using both reverse vaccinology and structural vaccinology approaches. A single immunogen was engineered that contained immunodominant regions from all three MenB sequence groups, which was able to elicit protective antibodies against all the tested variants of the MenB serotype [37]. Broadly neutralizing antibodies have also been identified for influenza, some targeting the highly conserved hemagglutinin stalk or other highly stable internal genes [38–41].

When a virus has several strains, another useful strategy for designing a single cross-protective immunogen is to develop a consensus sequence. This involves aligning a number of representative sequences and usually selecting the most common for a synthetic sequence. This is applicable to essentially any vaccine platform and has recently been utilized for H7N9 influenza, chikungunya and HIV [42–44]. A pioneering approach to epitope design

and selection was reviewed by Boberg and Isagulians who built on the observation that in natural HIV infection, drug resistant virus can elicit cellular immunity targeted at the mutated epitopes of the reverse transcriptase and other HIV enzymes [45]. Specific epitopes might be cross-protective for both wild-type and mutant virus or target only the mutated resistant virus. The resistant epitopes could be incorporated into many different design strategies and be used either as a therapeutic or prophylactic vaccine. In a later example, wild-type and mutant reverse transcriptase epitopes were fused to a lysosomal protein to alter the route of degradation. Mice inoculated with this chimera developed both antibodies and cellular immunity that were cross-protective for viruses with both the wild-type and mutant enzymes [46].

Other vaccine design approaches might similarly deserve consideration for antiviral vaccines. One new concept is based on finding commonalities across the viral life cycle. Recently demonstrated for RSV, this structural-based concept uses transitional conformation as the immunogen [47]. RSV has a fusion protein (F), which combines with the cell membrane. The F protein has prefusion and postfusion conformations, neither of which led to effective immunity. However, a stabilized model of the unstable transition state between the two conformations proved to be a potent and protective antigen for a vaccine in preclinical studies. In addition, the use of attenuated viruses as live vaccines is attractive because a replicating virus should elicit a more durable, broader and natural immune response than a subunit/inactivated vaccine approach. Although the possibility of viral reversion to wild-type exists, several groups have taken an approach to limit that possibility through the introduction of numerous, well-placed mutations. Accordingly, computer-aided design has been used to alter amino acid codons of an attenuated virus from those frequently used by the host to those infrequently used, while retaining the original amino acid sequence [48,49]. Such strategies could be applied to cocktails of attenuated phenotypes predicted to emerge based the mechanisms of the prevalent classes of antiviral drugs.

Evaluation

Once the immunogen is designed and delivery features are identified, the candidate vaccine needs to be evaluated for safety and efficacy. Often the initial evaluation is done in an animal model of the infection/disease. Ideally, an animal model should: use unadapted human virus, recapitulate both disease pathogenesis and the mechanisms of protection, replicate inoculum size and site of infection, and, finally, utilize a small, easy-to-handle species. In actuality, the ideal does not exist and compromises must be made. Clearly, more reliable methods for accurately predicting vaccine efficacy are needed. The key feature of a good animal model is its predictiveness. If go/no go decisions can be accurately made in the preclinical stages of development, the consequent savings in time and resources are tremendous. Once a candidate is identified, investment in clinical efficacy trials is a significant financial decision. Although this is critical for all vaccines under development, vaccines targeted to address the emergence of antiviral resistance will need to manage additional layers of complexity. Two issues that must be considered are how to utilize populations/sites in which antiviral resistance is a significant concern, and how to identify and evaluate endpoints that demonstrate 'antiviral resistance efficacy'.

On the research end, the advent of systems biology research is already revolutionizing the science of developing vaccines. Systems biology has been described as *'an interdisciplinary approach that systemically describes the interactions between all parts in a biological system, with a view to elucidating new biological rules capable of predicting the behavior of the biological system'* [50,51]. Systems biology can be used to identify correlates of protection and biomarkers that are predictive of the quality of the immune response, and may involve one or more of the 'omics' areas: genomics, transcriptomics, proteomics, lipid-omics and metabolomics. A study of the transcriptome of the yellow fever vaccine (YF-17D) using samples collected from two independent clinical studies provided an early example of the value of this type of analysis [52]. As this is a live-attenuated vaccine, it was not surprising that the transcription of a set of interferon-inducible genes, indicating the activation of the innate immune response, was induced early. They were part of a transcription signature that correlated with a YF-17D-specific CD8⁺ T cell response and also included a complement factor and a eukaryotic translation initiation factor. A separate signature that included B cell growth factor predicted the magnitude of the neutralizing antibody response. Another important study compared the human transcriptional responses seen with the live attenuated influenza vaccine (LAIV) and the inactivated counterpart, trivalent inactivated influenza vaccine (TIV) [53]. Responses were compared separately over three flu seasons and were the same for each vaccine and each season. By examining the results from vaccinees three days after vaccination, it was possible to distinguish those who had a robust response from those who did not. LAIV, like the live attenuated YF-17D, activated a set of type 1 interferon-inducible genes. Vaccination with TIV resulted in high titers of antibody and an enhanced number of antibody-secreting B cells. Although this indicates that TIV is more immunogenic than LAIV, they seem to be equally protective. When evaluating new vaccine candidates, once transcription patterns associated with protection are identified, it should be possible to down-select based on data from a Phase I clinical trial and save a great deal of time and expense in clinical testing. Application of this technology to signature patterns distinguishing the emergence of an antimicrobial-resistant form of a susceptible pathogen is just beginning.

Implementation: a new model for vaccination?

Utilization is one of the most critical problems to consider when designing a vaccine to address the emergence of antimicrobial resistance. All currently licensed vaccines are designed and developed for public health purposes. This existing model has evolved to be relatively simple and straightforward, but with little room for variation. Briefly the model relies on the fact that vaccines are intended for and available to entire populations, or at least large subsets of a population. In the USA, federal and state regulations and funding are in place to assure that all the relevant populations, usually determined by the Advisory Committee on Immunization Practices, have access to these vaccines, and thus the cost of a vaccine is an important factor to be considered. Additional federal and state regulations and funding assure that both ample supplies of vaccine are available and that the vaccines are utilized within a window of the recommended time deemed to be the most beneficial to both the person receiving the vaccine and the at-risk population. Noncompliance with vaccine utilization recommendations is handled on a state-by-state basis, but exemptions are usually

tolerated within a narrow spectrum (e.g., on the basis of health status or religious beliefs). Noncompliance outside of that spectrum can result in limitations of other state benefits such as the ability to attend public schools or state-supported day care systems. This model is further reinforced through demonstrable successes and a culture of moral imperative. It has had a significant impact on the health of the general public and is projected to continue to do so as current vaccines are implemented worldwide [54,55]. The question is: does this model need to be used for the development of all vaccines?

Historically, deviation from this public health model of vaccine utilization, supply, delivery and funding is rarely considered or discussed. One major exception is the concept of therapeutic vaccines, for which the oncology community has been at the forefront of research and development. In this 'exception' model, vaccines are not developed for public health strategies but rather as a personalized approach to augment the control of cancer in a defined disease area or individual. Discussions of alternative vaccine models for public health consideration have been quite limited. One such discussion has briefly focused on a better definition of the 'public' who would personally most benefit from receiving vaccines. Built upon increasingly available technological opportunities, the ability to catalogue 'signature profiles' would theoretically preidentify the most likely outcome of a vaccination on an individual level. Initial data have suggested that a relatively simple set of signatures within a population could be predictive of responses to a specific vaccine. Such a correlation could logically allow for more active decisions regarding individual vaccination. This approach is in its early research stages and is taking advantage of the emerging knowledge and understanding of genetic profiles and their associated immune responses [56,57]. While intriguing, this concept is hard to envision in its implementation stage or as a model for public health, but it does begin to tilt the balance between public health and personal health through selective prophylactic vaccination.

We can build upon the definition of an 'at risk' public if we look at the development of new viral vaccines for which antiviral resistance is a primary target of interest, rather than a potential by-product. A focus on pathogens for which we have active development or access to antivirals would be of most interest to explore. For illustrative purposes, this discussion will focus on three pathogens: hepatitis C, HIV and CMV. Despite the importance of antiviral drugs in controlling these infections, the public health goals of eliminating these diseases can never be met with antivirals alone. Yet, it could be argued that the introduction of HIV and hepatitis C vaccines under the current vaccine model (e.g., as a low cost and required adolescent or pediatric vaccine) will be difficult. However, in both cases there are subsets of 'at risk' populations for whom the personal health benefit, the associated health benefit of those within this demographic, and the reduction of significant and long-term health care and related societal costs would make the development and implementation of these vaccines under a 'novel' public health model quite attractive. Add to that the recognition that emergence of resistance of these highly mutable viruses will require the continuous development of newer drugs/drug combinations, at predictably higher costs, and the possibility of emergence of newer viral strains with properties that may result in the broadening of the definition of 'at risk' groups, and a new concept of 'vaccines for public health' begins to emerge.

In the case of CMV, the populations of interest are either the adolescent female, for prevention of congenital CMV, or the solid organ and stem cell transplant recipient. Both of these populations have their advocates, but for the purpose of this discussion on controlling the emergence of resistance, the relatively small health market of solid organ and stem cell transplant patients will be highlighted. CMV-associated infections following transplantation are strongly correlated with transplantation failure. In addition, the importance of CMV donor seropositivity in solid organ transplantation has been well-documented as a negative variable in the survival of transplant patients [58]. A recent report of CMV serostatus as a prognostic indicator of survival of acute leukemia patients after allogeneic stem cell transplants similarly suggests the negative effects of CMV-positive serostatus on overall patient survival [59]. Prophylactic treatment with antivirals such as acyclovir and ganciclovir began in the early 1990s following trials that demonstrated a significant increase in survival of such patients [60–62]. By the mid-1990s, emergence of drug resistance was noted and found to be associated with late morbidity [63,64]. Like the preceding HIV/HCV discussion, the primary value of developing a CMV vaccine would be the personal benefit for a subset of ‘at-risk’ populations. Arguments could be made that although the introductory market would be relatively small, global market expansion, with perhaps larger numbers deemed ‘at-risk,’ could be feasible. For HIV and HCV vaccines, tiered pricing, subsidies and incentives suggest a viable, but complicated, cost-effective vaccine would be possible [65–67]. If such an approach proved successful, the secondary benefit could be the expansion of the definition of ‘public health’ to include an economic aspect, incorporating such factors as lessening of hospital stays, reduction in drug toxicity complications, reduction in the development of newer generation and more expensive antivirals, and perhaps decreasing the burden of CMV reactivation in an immunocompromised patient.

Conclusion

For a subset of viral diseases, the emergence of antiviral resistance would have devastating consequences. The development of viral vaccines for the primary purpose of reducing the threat of antiviral resistance is a concept that is worthy of serious consideration. Although vaccines for public health usage have been overwhelmingly successful, some viral infections may require a new approach that targets smaller, at-risk groups. In the short term, the motivation to develop such vaccines is met with several very real obstacles. While research approaches suggest that designing these vaccines would be technically feasible, the ability to implement them under our existing models may be the factor most limiting to movement in this direction. Therefore, as technology continues to improve, a new model of vaccination based on personal health may present an effective strategy for future vaccine research and development.

Future perspective

Do the will and momentum to change the existing vaccine model exist? The ability to move forward remains complicated by our vaccine utilization policies. Whereas the existing policies were developed for low cost products and high volume usage, vaccines for smaller, well-defined populations and for personal health purposes, including antiviral resistance as a primary end point, will most likely require a model of high cost and low usage, at least

initially. This is not to say that the current policy is wrong, but simply that the need for these products does not easily adapt to such a model. There are other models within the health care sector for low usage, higher cost products for selective populations that are willingly and justifiably used. Most of these models, however, are in the therapeutic sector, and none involve vaccines. Historically, the health sector has economically underestimated the use of interventions that have future value. This has been particularly true for vaccines for which the cost/benefit ratio is a key component for public usage. Hence, one suggestion is to consider these products discussed above not as ‘vaccines’ but more as ‘personal immune interventions’ (Piis). The concept of Piis frees one from the history associated with current vaccine models and suggests it may be beneficial to consider a new market dynamic for prophylactic health, which also has value to the public albeit in the long term. Piis could target selected markets, be used under prescription, and be price-valued under market standards. In such a model, personal prophylactic health would be the driver and public health, including the health of the economy, would be a by-product.

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EXECUTIVE SUMMARY

- While antibiotic resistance is a well-known issue in health care, antiviral resistance is rarely mentioned as an issue of concern. One of the main reasons for this discrepancy is that viral vaccines have been very successful.
- However, there are several infections for which antiviral resistance is becoming a serious problem. These include both infections for which a vaccine is available (e.g., influenza) and infections that do not have licensed vaccines (e.g., HIV). Although combining several antivirals has been shown to be a useful treatment strategy, arguably, efficacious vaccines would be an even more effective way to combat drug resistance.
- Vaccines targeting pathogens for which antiviral resistance is a concern will face a number of challenges in design, evaluation and implementation. New areas of research, such as structural biology, may provide opportunities for innovation in some of these areas.
- Although the public health model of vaccination has been extremely effective in the past, it may not be useful to develop all vaccines at low cost for large populations. A new implementation model may be worth consideration for vaccines focused on addressing antiviral resistance. These vaccines may target smaller groups of people who are at high-risk for complications from infection, and therefore, they may be considered ‘personal immune interventions.’

Figure 1.

Vaccines have had a tremendous impact on the control of viral infections in the USA [4–11].

Table 1

FDA-approved control measures for common viral infections.

Virus	Disease	Vaccine?	Vaccine type	Direct antiviral?	Host-targeted antiviral?	Clinical resistance?
Adenovirus	Rhinitis, bronchitis	-	-	-	-	-
Chikungunya	Fever and arthralgia	-	-	-	-	-
CMV	Congenital, transplant recipients	-	-	-	-	-
Dengue	DF, DHF, DSS	-	-	-	-	-
Ebola	Hemorrhagic fever	-	-	-	-	-
Hep A	Hepatitis	-	IN	-	-	-
Hep B	Hepatitis, hepatic carcinoma	-	R	-	-	-
Hep C	Hepatitis, hepatic carcinoma	-	-	-	-	-
HIV	AIDS	-	-	-	-	-
HPV	Genital warts and cervical cancer	-	R	-	-	-
HSV	Cold sores, genital herpes, encephalitis	-	-	-	-	-
Influenza	Flu	-	LA, IN	-	-	-
Japanese encephalitis	Encephalitis	-	IN	-	-	-
Measles	Measles	-	LA	-	-	-
Mumps	Mumps	-	LA	-	-	-
Polio	Polio	-	LA, IN	-	-	-
Rabies	Rabies	-	IN	-	-	-
Rotavirus	Diarrhea	-	LA	-	-	-
RSV	Bronchiolitis, pneumonia	-	-	-	-	-
Rubella	German measles	-	LA	-	-	-
VZV	Chicken pox and shingles	-	LA	-	-	-
West Nile virus	West Nile fever and CNS disease	-	-	-	-	-
Yellow fever	Yellow fever	-	LA	-	-	-

A listing of common viral diseases and the interventions currently available for their control. The final column indicates whether or not antiviral resistance has emerged as a clinical problem [1–3].
 DF: Dengue fever; DHF: Dengue hemorrhagic fever; DSS: Dengue shock syndrome; IN: Inactivated; LA: Live attenuated; R: Recombinant; RSV: Respiratory syncytial virus; VZV: Varicella zoster virus.