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Short communication

An opportunity to incentivize innovation to increase vaccine safety in the United States by improving vaccine delivery using vaccine patches

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ABSTRACT

Vaccines represent cost-effective and safe interventions that provide substantial health and economic benefits to individuals and populations. The US vaccine enterprise that supports all aspects of immunization continues to encourage innovation. Despite some limited historical recommendations to create a fund to support investments in vaccine safety, and recent legislation that supports innovation for new vaccines (the 21st Century Cures Act, Public Law 114–255), to date the US lacks financial incentives to fund innovation in vaccine delivery technologies. Building on separate reviews of the US Vaccine Injury Compensation Program (VICP) and the state of development of vaccine patches as an innovative vaccine delivery platform, we suggest an opportunity to allocate some VICP Trust Fund resources to prevent future VICP claims by creating a new incentives fund to support translational studies for improving vaccine delivery technologies. We identify shoulder injury related to vaccine administration (SIRVA) as a test case.

1. Introduction

Vaccines represent cost-effective (sometimes cost-saving) and safe interventions that provide substantial health and economic benefits to individual Americans and the population [1,2]. Significant financial support derived from Americans sending dimes to President Franklin D. Roosevelt and the National Foundation for Infantile Paralysis (now the March of Dimes) led to the commercialization of polio vaccines in the 1950s [3], which have yielded substantial US health and financial benefits over many decades [4]. Polio vaccine introduction across the US also helped to establish national enthusiasm for vaccines, and early development of the current US vaccine enterprise. One 1997 study estimated that US government financial investments contributed substantially to the development and first approval of more than two-thirds of the new vaccines approved in the US between the mid-1970s and mid-1990s [5].

Notably, the early American experience with polio vaccine introduction also helped to establish the foundations of some of the regulatory elements of the US vaccine enterprise and set a legal precedent for compensation of vaccine-associated injuries [6,7]. Successful lawsuits that built on this legal precedent and pursued claims against pertussis vaccine manufacturers in the 1980s led to a significant drop in the number of pertussis vaccine manufacturers [6]. The resulting consolidation of the market and the increased liability led to a nearly 10-fold increase in the price of pertussis vaccine as the one remaining manufacturer passed on the costs of its liability insurance to purchasers [6]. This situation raised concerns for vaccine purchasers about vaccine manufacturers exiting the market completely, and about the stability of the vaccine enterprise overall [6]. The US government responded to the liability issues in the mid-1980s by establishing the US Vaccine Injury Compensation Program (VICP) [8].

In the US, the vaccine enterprise that supports all aspects of immunization continues to encourage innovation and investment in the development of new vaccines demanded by Americans. However, despite some limited historical recommendations to create a fund to support investments in vaccine safety, and recent legislation that supports innovation for new vaccines (the 21st Century Cures Act, Public Law 114–255), to date the US lacks financial incentives to fund innovation in vaccine delivery technologies or other incremental improvements in existing vaccines [9]. A recent review of vaccine patches identified sufficient maturity of the technology to consider vaccine patches as a platform, but highlighted the lack of financial incentives as a barrier to the commercialization and licensing of vaccine patches as new products [10]. Briefly, vaccine manufacturers would need to make substantial investments to (i) conduct large-scale clinical trials, (ii) adopt

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and scale up new manufacturing capacity to make the patches under Good Manufacturing Practices, and (iii) manage the complicated regulatory submissions required for new platforms and new vaccine products [10].

A separate recent review about the now 30-year experience with the US VICP showed the relatively low rate of vaccine-associated injury claims overall, and reported on the strong financial performance of the VICP Trust Fund [8]. That review also identified shoulder injury related to vaccine administration (SIRVA) as a claim related to all injectable vaccines and as a signal of an important safety category related to vaccine delivery [8]. We reiterate here the importance of the VICP in providing compensation for vaccine-associated injuries and protecting manufacturers from liability for all vaccine-associated injuries, including SIRVA [8].

In this perspective, we suggest an opportunity to create a new US funding mechanism that targets providing financial incentives for vaccine manufacturers to invest in the commercialization of innovative vaccine delivery technologies that will reduce or eliminate SIRVA. Specifically, we suggest the allocation of a fraction of the existing VICP Trust Fund and/or future diversion of a fraction of expected incoming vaccine excise taxes to create a new incentives fund to support translational research and development of vaccine delivery technologies that show some promise for reducing or eliminating future VICP claims. We suggest using SIRVA as a test case for exploring the use of a fraction of VICP Trust Funds to support activities that will reduce future VICP claims.

2. US incentives for developing new vaccines

For this perspective, we assume that readers appreciate the complexity of the US vaccine enterprise and challenges with vaccine financing [11,12]. Briefly, the US market divides vaccine financing into the private sector (from private insurance) and the public sector. In the public sector, the Vaccines for Children (VFC) program guarantees financial support for all eligible children to receive vaccines recommended by the US Advisory Committee on Immunization Practices (ACIP). The VFC supports public purchase of nearly half of all pediatric vaccines through public (i.e., US government) purchase [13].

The public purchase of vaccines ensures the existence of a large market for vaccines recommended for routine use. The Act that created the VFC stipulated that the public price of a vaccine before application of the excise tax cannot increase more than the public price of the same vaccine on May 1, 1993 after adjustment for inflation using the consumer price index [13]. This requirement maintains constant real pre-excise tax public prices for all vaccines available as of May 1, 1993. With a constant nominal excise tax of $0.75 per vaccine antigen for the VICP Trust Fund added per dose [8], the lack of changes for inflation for the excise tax implies a slight decline in the real total public price over time for vaccines that existed in 1993. In contrast, the US private market pre-excise vaccine price is not similarly constrained (although the same nominal $0.75 per vaccine excise tax applies), and thus manufacturers can potentially recover some costs associated with improvements and/or post-market activities for existing vaccines in the US from the private sector. This represents an important opportunity for vaccine manufacturers to cover the costs of post-market research, some marginal improvements in production processes, and/or product-related communication activities, including investments made to counter claims of harms associated with vaccines (e.g., to defend their products against false claims).

The US vaccine market includes substantial barriers to entry (e.g., high pre-licensing investments only recoverable after commercialization and successful marketing), high regulatory costs (i.e., licensing, compliance), liability, and demands for high volumes at low prices from the largest buyer (i.e., the US government through VFC). The imperfect market conditions favor the economies of scale that come with one or a few vaccine producers (monopolies or oligopolies) serving the entire market for many vaccines. The lack of competition reduces incentives for a vaccine manufacturer to invest in innovations in incremental changes that will not affect its market share. Thus, although technological innovations (e.g., adjuvants, enhanced potency, vaccine vial monitors, new vaccine delivery technologies) could potentially make existing vaccines more effective, cheaper to produce, less likely to be wasted, and/or easier to administer, limited recognition of the potential benefits of these improved products combined with the cost and time of developing them to licensure can serve as a barrier to investment in the US market [9]. However, when the market size and potential return appears justifiable to the manufacturer, then this leads to notable exceptions like the development of Shingrix™. GSK invested in the development of two-dose, adjuvanted Shingrix™ despite the existing licensure and use of one-dose Zostavax™, which led to a substantially more effective vaccine that offered longer-lasting protection, became the preferred vaccine, and drove Zostavax™ out of the market [14]. Similarly, Dynavax Technologies Corporation felt encouraged to develop a hepatitis B vaccine (HepB-CpG or Heplisav) requiring only 2 doses for a primary series, to compete with the prevailing other hepatitis B vaccines that require 3 doses. While the ACIP did not give a preferential recommendation for HepB-CpG, its recommendations made the new vaccine an equal alternative to other vaccines [15].

Part of the success of the US vaccine enterprise comes from the ability of vaccine manufacturers to financially recover their investment of resources for the development of new vaccines. The costs of developing a new vaccine typically exceed more than $1 billion (current US dollars) spent over approximately 10 years of time for research, regulatory testing and compliance, and the development of mass production capacity to bring a new licensed vaccine product to market [16,17]. The complexity of the science, and the high costs and uncertainties about overcoming multiple challenges to cross the translational "valleys of death" (i.e., the large gaps between basic scientific research and widespread use of novel therapeutics) [18,19] limit interest in investing in vaccine innovation to some degree. Specifically, manufacturers must overcome multiple challenges, including the need to determine what is a protective immune response and demonstrate the ability of the vaccine product to induce it. This typically initially involves animal studies, and then conducting progressively larger, time-consuming, costly, and often unsuccessful human clinical studies to demonstrate safety and efficacy. Most importantly, these time-consuming and expensive steps must be repeated for substantial modifications of existing vaccines, with the modified product required to minimally show non-inferiority in safety and/or effectiveness compared to the existing product, and to demonstrate measurable benefit, in order to receive a preferential recommendation by the ACIP. Manufacturers who undertake these efforts do so at-risk (i.e., with no guarantee of a benefit), which reduces enthusiasm for investing in incremental improvements.

In addition, in spite of the VICP, US vaccine manufacturers continue to face assertions about the dangers of vaccines, in many cases made by individuals or organizations who seek to benefit financially. This leads vaccine manufacturers to invest resources that they might otherwise spend on innovation on defending the safety of existing products instead. In addition, the possibility of opening up new lines of attack by modifying vaccines also decreases incentives to innovate on existing products, particularly given the high costs of making changes associated with regulatory activities, unless the innovation results in a new vaccine.

One option that vaccine manufacturers pursue to develop new vaccines relates to the creation of combination vaccines, which

combine two or more existing vaccines into a single product. With respect to the FDA licensing and any subsequent ACIP recommendation and inclusion of the vaccine in VFC, each new combination becomes a new vaccine (even if the vaccine combines two separately-licensed existing vaccines). This implies development costs associated with conducting clinical trials to show safety and efficacy of the combination and non-inferiority for each component included in the combination product compared to delivery in a non-combined or less-combined formulation. The US treats new combination vaccines as new vaccines, which allows for the establishment of a new public price (i.e., not anchored on a May 1, 1993 price since the vaccine did not exist then). The opportunity to set a new (higher) price incentivizes innovations that enable combination vaccines, and can increase overall national spending on vaccines [20]. The need to overcome intellectual property rights issues around developing combination vaccines that use components from different manufacturers and to streamline the regulatory issues around combination vaccines can represent barriers to increased development of combination vaccines.

Historically, in the face of an uncertain or non-existent market for regular demand for a vaccine, the US government has successfully created public-private partnerships. For example, public-private partnerships supported purchases of smallpox and anthrax vaccines to address bioterrorism concerns (spearheaded by the Biomedical Advanced Research and Development Authority (BARDA), part of the HHS Office of the Assistant Secretary for Preparedness and Response) [21]. The US government also devotes significant resources to support research and development of vaccines for emerging infectious diseases when faced with a threat (e.g., HIV starting in the 1980s, with US spending of over $10 billion between 2000 and 2017 and no licensed vaccine to date despite this investment [22], pandemic influenza [23], and more recently Ebola and Zika [24] and now Coronavirus (Public Law 116–123, Coronavirus Preparedness and Response Supplemental Appropriations Act, 2020, enacted March 6, 2020). The US also makes substantial investments in the selection and production of the annual influenza vaccine [25], but these investments still may not support the types of innovation required to obtain an optimal (or significantly improved) vaccine [26]. In addition, to address the lack of incentives to develop vaccines for highly uncertain and potentially small expected markets for emerging infectious diseases, which may lack the promise of commercial profitability, the Coalition for Epidemic Preparedness Innovations (CEPI) launched in 2017 using a new international funding model [27] that includes support from the US-based Bill and Melinda Gates Foundation.

3. Vaccine delivery technologies

The exploration of options for human vaccine administration includes the consideration of all possible routes of entry into the body and a wide range of strategies [28]. Currently, using a syringe and needle to inject vaccine through the skin barrier represents the dominant vaccine delivery technology, although the US market includes a limited number of licensed oral (e.g., Rotarix™, an oral rotavirus vaccine) and intranasal (e.g., FluMist™) vaccines [29].

Not all vaccines represent candidates for oral or intranasal administration. However, in the US, some vaccines take advantage of these routes of transmission using live, attenuated viruses or bacteria. The development of US-licensed FluMist™ followed many years of US government investment [30] in research to develop a cold-adapted, live, attenuated influenza vaccine. FluMist™ delivers influenza vaccine using a device that aerosolizes vaccine into the nasal passages and thus eliminates needle-related risks (including the disposal of sharps). Approved in the US in 2003 [31], FluMist™ offered easy delivery and captured increasing market share [32]. However, it subsequently faced some challenges unrelated to the route of administration with respect to its flu strain match, which led to relatively lower efficacy compared to other available (injectable) flu vaccines. The lower efficacy affected its inclusion in the list of vaccines recommended by the ACIP and covered by VFC funds for public purchase for the H1N1 strains for the 2016–17 and 2017–18 flu seasons, although subsequent changes in the vaccine led to a full recommendation for use again in later flu seasons [33,34]. The experience with FluMist™ should serve as a cautionary example for other novel delivery technologies (e.g., vaccine patches), which could similarly face efficacy challenges and market share impacts that may relate to differences between the strains in the vaccine and circulating strains or other adjuvants or excipient choices and not the delivery mechanism itself. Past experiences with other failed attempts to develop vaccine products that use alternative delivery technologies also influence vaccine manufacturer decisions about these types of innovations (e.g., aerosol [35] and transcutaneous [36] measles vaccine delivery technologies that did not pass the clinical trial criterion for non-inferiority in clinical trials, and the Swiss experience with increased incidence of Bell's palsy associated with its intranasal inactivated 2000–2001 influenza vaccine that contained *Escherichia coli* heat-labile toxin as a mucosal adjuvant [37]).

Historical approaches to develop needle-free delivery technologies for otherwise injectable vaccines led to numerous designs of multiuse nozzle jet injectors, which found widespread use in mass campaigns [28]. However, the US discontinued all use of multiuse nozzle jet injectors due to the potential for bloodborne pathogen transmission risks (from insufficient cleaning between multiple uses) [28]. Subsequent development of disposable-syringe jet injectors led to a functional alternative in the US, but their use can only occur with vaccines for which the vaccine label explicitly allows use of the specific device [28]. Using disposable-syringe jet injectors thus increases the cost of delivery, both to get the indication included on the label (e.g., Afluria seasonal influenza vaccine [38]) and to pay for the incremental cost of the device and disposable components compared to syringe and needle). To date, these devices do not see widespread use in the US. However, following the US Food and Drug Administration approval of Seqirus Afluria™ vaccine administration by the PharmaJet Stratis™ device for adults in 2014 [39], the use of this needle-free vaccine delivery device has increased. New biomaterials and technologies also suggest significant promise for vaccine delivery using vaccine patches (despite a long path with some notable failures [10,40]), which deliver vaccines through the skin using arrays of submicron projections, although no licensed vaccine patch exists to date in the US.

In the case of the US, any vaccine manufacturers that add a feature to a vaccine product that requires them to use additional resources, but which exclusively benefits downstream users (e.g., ease of delivery, less waste) will expect to recover the costs for that feature in the vaccine price. Thus, for injectable vaccines, vaccine manufacturers would need to see a significant signal from the market that indicates substantial demand to invest in an alternative delivery technology for an existing vaccine product. In the context of the current US market, no clear incentives exist currently for vaccine manufacturers to invest in innovations that increase their costs but may save costs in other parts of the health system.

4. Incentives to develop non-injection delivery technologies for injectable vaccines

Many opportunities compete for scarce resources for innovation. One opportunity to explore priorities for innovation can come from the review of VICP claims, with an eye toward investing now

in strategies that offer the potential to reduce future VICP claims. Specifically, to the extent that innovations that improve existing vaccines and/or vaccine delivery technologies address an identified vaccine safety issue, these innovations offer the potential to reduce future VICP claims. Our prior review of VICP claims identified SIRVA as an increasingly important injury category, and one that relates directly to the delivery of injectable vaccines [8]. Notably, consistent with the highest number of vaccine doses annually given for influenza (i.e., over 100 million doses), we reported the highest numbers of VICP claims for influenza vaccine [8].

Expanding on those findings, Table 1 shows the US experience with VICP SIRVA compensated claims since 2011, which increased over time. Nearly all (1590/1600, 99.4%) of the SIRVA compensated claims involved adults (18 years and older), with the percent of total numbers of compensated claims and the percent of total VICP compensation paid associated with SIRVA increasing over time. Since 2011, VICP SIRVA compensation to petitioners has exceeded $168 million (as of March 12, 2020). Table 1 also reports 1,385 SIRVA-associated claims pending as of March 12, 2020 (some of which will get dismissed when adjudicated), of which 1,185 pending claims relate to the administration of influenza vaccine. If VICP SIRVA claims continue to lead to compensation on the order of around $40 million per year, then we can anticipate cumulative US spending of over $500 million on VICP SIRVA claims by 2030. Table 1 also shows that most of the SIRVA claims involve influenza vaccine delivered to adults, which suggests a significant opportunity to avoid VICP claims and pay-outs associated with elimination of influenza-related injection injuries. Recognizing the mounting costs of these injuries and that vaccine manufacturers currently lack adequate incentives to fully invest in the research and development needed for promising incremental improvements for existing vaccines and vaccine delivery methods [9], we consider the creation of a new incentives fund for reducing future SIRVA claims. We note that while reducing injections also provide multiple additional benefits that fall outside of the VICP (e.g., eliminating occupational needle-stick injuries, reducing sharps disposal requirements that affect the health system, enabling vaccine delivery by personnel who do not need training for delivering injections, including self-administration), we ignore those likely external benefits.

5. Creation of new incentives for innovation to reduce vaccine delivery-associated injuries

A review of the VICP showed that the current level of the Vaccine Injury Compensation Trust Fund (VICTF) continues to grow at a rate such that inflows from the excise taxes and interest income received by investment of the funds by the Department of the Treasury marginally exceed expenditures, which include payments made for injuries, legal representation, and expenses associated with administration of the program [8]. We propose, based on past experience, that the amount of the VICTF set aside to ensure the provision of payment to individuals entitled to compensation for vaccine-associated adverse events could be leveled off somewhere in the range of $2 to 3 billion (i.e., nearly $1 billion held against existing claims in the system given the 2–3 year delay to process claims and a $1 to 2 billion reserve). Now that the fund has reached nearly $4 billion, we suggest that the amount above the necessary level could go to a fund that would be available to support the costly translational studies (i.e., Phase 2 and 3 clinical trials, post-market surveillance) needed to support the commercialization of vaccine products designed to prevent potential future vaccine injuries. This could operationally occur by diverting some fraction of the inflow of new excise taxes into a newly created research and development fund that would support innovation for vaccines for which the excise taxes exist (i.e., it would preclude the use of the funds for new vaccines) and only divert the fraction that maintains the VICTF at the necessary level (i.e., accounting for the interest revenue on the fund as well). The Department of the Treasury would continue to invest the anticipated level amount of the existing VICTF, such that interest income would continue to accrue. The Department of the Treasury could similarly invest any of the funds held for this newly created innovation fund that remain unallocated. Designation of the funds to specifically address the existing barriers to the performance of research and development needed for the prevention of future VICP claims appears most consistent with the original intentions of the VICP. The proposed changes would use funds to provide manufacturers with incentives for improvement of existing vaccines and delivery technologies.

A process would need to be put in place to evaluate and allocate research and development funding. We would suggest the process should involve the Health Resources and Services Administration (HRSA) Division of Injury Compensation Programs (DICP), which administers the VICP, to ensure that the proposed research and development investments hold reasonable promise of addressing real improvements in vaccine safety that will reduce future VICP claims. The potential for risk-risk trade-offs should also be considered (e.g., evaluation of whether a proposed change aimed at reducing or eliminating one type of injury or risk may increase another type of injury or risk). This proposed concept offers the opportunity to reward existing manufacturers who supply vaccines to the US market for making investments that will make exist-

Table 1
Status of US Vaccine Injury Compensation Program (VICP) claims compensated each fiscal year associated with shoulder injury related to vaccine administration (SIRVA) [46] (Division of Injury Compensation Programs, personal communication, March 2020).

Fiscal Year	Number of cases compensated for petitioner under age 18 years old	Number of cases compensated for petitioner age 18 years or over	Total cases compensated	SIRVA claims compensated/Total claims compensated (%)	Total petitioner compensation paid associated with SIRVA ($)	Percent of total VICP petitioner compensation paid associated with SIRVA
2011	1	6	7	7/251 (3%)	1,738,785	0.8%
2012	1	3	4	3/249 (2%)	315,674	0.2%
2013	1	10	11	10/375 (3%)	1,867,457	0.7%
2014	0	39	39	39/365 (11%)	5,325,246	2.6%
2015	3	122	125	122/508 (25%)	17,497,672	8.6%
2016	0	260	260	260/689 (38%)	29,869,178	13.2%
2017	2	286	288	286/706 (41%)	32,231,058	12.8%
2018	0	284	284	284/522 (54%)	26,699,487	13.4%
2019	2	407	409	407/653 (63%)	35,745,300	18.2%
2020*	0	173	173	NA	16,810,818	

* Adjudicated claims as to 3/12/2020 for Fiscal Year 2020 (i.e., October 1, 2019 through September 30, 2020). As of 3/12/2020, DICP also reported a backlog of 1,385 pending SIRVA claims (i.e., all accumulated SIRVA claims not yet adjudicated, including some claims for cases that will be dismissed when adjudicated).

ing vaccines and their delivery safer for Americans and prevent future VICP claims. The process to allocate and monitor the funds could involve the establishment of a review process by the National Institutes of Health or National Vaccine Program Office, perhaps concurrent with or following review by HRSA DICP that any proposed research includes the potential to reduce compensable vaccine injuries.

Changing the proposed incentive into a real incentive will require new legislation. We recognize that opening up legislation comes with both promise of improvement and peril of diversion given the nature of the US democratic system. While creating the proposed incentive represents a relatively simple concept that could occur with small changes, we recognize that any change would require sufficient consensus for the legislation to pass. In addition, any changes should not disrupt the primary function of the VICP of providing payment to individuals entitled to compensation for vaccine-associated adverse events, including SIRVA [41]. We suggest that such an incentive could lead to innovations that reduce vaccine-associated injuries and improve the safety of vaccine delivery for Americans without any net increase in taxes. We also suggest that such a mechanism could support the costly clinical trial studies that currently serve as a barrier to the advancement of vaccine delivery technologies like a vaccine patch platform [10].

In addition to creating incentives for the development of vaccine delivery technologies like vaccine patches, we suggest the mechanism of using a sustainable fraction of VICP Trust Funds to create a financial incentive to reduce future SIRVA claims could involve studies that identify effective interventions to train healthcare workers and pharmacists who deliver vaccine injections to avoid shoulder injuries. The proposed mechanism could also potentially be used to support studies that would reduce other types of vaccine-associated injuries, although in this proposal, we suggest a modest test of the concept. Overall, we hope that greater awareness of SIRVA will improve training for health personnel who deliver injectable vaccines, but we recognize that SIRVA represents a vaccine-associated injury that should be covered by the VICP.

We also recognize the potential role of other types of incentives to motivate the development of alternative vaccine delivery technologies, including vaccine patches. For example, pull mechanisms, such as priority review vouchers, guaranteed purchase commitments, and/or preferential ACIP recommendations, if possible, could also help, and public-private partnerships could help to share costs and risks [8].

6. Discussion

Although we focused on the US market, we recognize the global market for vaccines, and that other countries benefit from US investments in vaccine innovation and Americans benefit from vaccines developed by researchers supported by other countries. We focused on US interests only in this perspective for several reasons.

First, while we recognize the importance of US investments in vaccines to promote global security, we believe that incentives for innovation need to benefit the US market. In addition, we are most familiar with the US vaccine enterprise. We encourage colleagues in other countries to consider the opportunities that their national governments may offer to incentivize similar investments.

Second, while US development agencies and private sector donors invest in organizations like Gavi, The Vaccine Alliance, which strive to promote faster adoption of vaccines and/or greater vaccine use in lower-income countries [42], this represents an outflow of US resources. In addition, although increased demand for products leads to lower prices in normal markets (i.e., increased demand allows existing buyers to share in the benefits of lower prices that occur with economies of scale), that does not generally occur in the global vaccine market. Notably, the global vaccine market includes tiered pricing, which enables earlier adoption and greater global use of the vaccines created and licensed in developed countries into lower-income countries, by allowing the lower-income countries to purchase the vaccines at lower prices than those paid in industrialized countries [43,44]. Tiered pricing can be accomplished by using existing production capacity for already-developed products to sell the vaccines at prices that reflect the marginal cost of production, making them affordable for developing countries who will or can only purchase at a lower price, or facilitating technology transfer from manufacturers in relatively higher-income countries to manufacturers in lower-income countries who can produce the vaccines with significantly lower production costs. However, since maintaining high prices for vaccines (and other pharmaceutical products) serve as the means for manufacturers to recover the costs of research and development in the US (as a market that values innovation), tiered pricing means that buyers in markets that support innovation do not realize the benefits of sharing these costs with buyers in other markets [11].

Third, despite the potential for US investments in vaccine innovation to drive global vaccine markets, US-based vaccine manufacturers play a relatively small role in the global market for vaccines, largely due to domestic concerns about prices and global tiered pricing [11,43]. In the US, which continues to pay higher health care costs per capita relative to other high-income and often better performing health systems, public concerns about health care costs can drive decisions. Congressional hearings in the early 1980s notably contributed to US-based vaccine manufacturers' decisions not to participate in global markets that demanded tiered prices [43]. Thus, instead of seeing a large number of vaccine manufacturers competing with each other and supplying products with tiered prices to different markets, the vaccine market is highly segmented and characterized by monopolistic or oligopolistic suppliers who generally sell to relatively few (i.e., oligopsonistic) large buyers, like the VFC program in the US, the Pan American Health Organization revolving fund for most other countries in the Americas, and UNICEF for developing countries. Thus, the vaccine market includes relatively high-priced vaccines targeted at relatively high-income markets (e.g., single dose, combination vaccines) and lower-priced multi-dose vaccines for relatively lower-income countries. Often a single manufacturer (or a decreasingly small number of manufacturers) serves the specific market [11,12,45]. Overall, while tiered pricing offers the benefits of allowing lower-income countries to purchase vaccine at a price that they can afford, the financing for innovation falls to the countries that can and choose to afford it.

Despite any challenges, we hope this proposal will lead to further discussion by a broad range of stakeholders about the potential to create incentives that will help to improve the safety of vaccine delivery and prevent some compensable vaccine injuries. We also hope that greater awareness of SIRVA will improve training for health personnel who deliver injectable vaccines, and that this discussion will reaffirm the importance of the VICP with respect to providing compensation for SIRVA and protecting vaccine manufacturers from SIRVA liability.

CRediT authorship contribution statement

Kimberly M. Thompson: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing - original draft, Writing - review & editing. **Walter A. Orenstein**: Conceptualization, Writing - review & editing. **Alan R. Hinman**: Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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