A Roadmap to a Safety First Agenda for the National Vaccine Program: Suggestions for the Draft National Vaccine Plan from a Patient Safety Perspective

Submitted by SafeMinds
for Public Comment to NVPO
through NVAC and IOM

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Overall Comments on the Draft NVP

Global comments: Our primary concern in submitting comments on the draft National Vaccine Plan of 2008 (NVP or Plan) is with patient safety and the elements which should be in place to support an adequate vaccine safety system. While "safety" and "risk" are mentioned throughout the document, the Plan remains deficient in ensuring patient safety commensurate with the prominent role vaccines play in medicine and their potency as long acting medicines with known side effects. The safety components of the Plan are characterized by inadequate resources, weak infrastructure, and insufficient checks and balances. The Plan must embrace the principle of *Safety First* rather than viewing safety as a minimum standard that is reluctantly addressed only to generate public buy-in to the official vaccination promotional program. Safety must be a goal in its own right, outside the context of risk/benefit. Reduction in adverse outcomes must be accomplished irrespective of the benefits which vaccines may bring. Vaccine safety extends beyond monitoring of adverse events following immunization (AEFIs) or calculating rates of specific acute, short-term adverse side effects in small pre-licensure studies. Safety should underpin all scientific and policy activities. Science goals should encompass rigorous identification of adverse outcomes from vaccination, prevention of adverse outcomes, reduction in their severity, their treatment, and understanding why adverse outcomes occur in certain individuals, that is, mechanisms and susceptibilities. Requisite resources and authority must be instituted for accomplishing these tasks. Policy must incentivize safety first practices through provisions for informed consent by patients and parents, objective and clear communication of scientific evidence on risk/benefit, removal of conflicts of interest, strengthening the safety net for compensation, holding manufacturers accountable for unsafe products, and prioritizing safety in decision-making when science has not reached consensus.

Comments on Goals 1, 4 & 5: While Goals 1, 4, and 5 use the word "safety" or "safer" several times, the titles, indicators and objectives make it clear that the focus is on creation of more vaccines for more diseases, extending vaccines to more populations, and inventing more effective vaccines. With the exceptions of targeting safer injection technologies in Goal 1 and safer delivery mechanisms in Goal 1, safety improvement is not a priority in that it is never assigned a progress target and is not included in the Goal indicators sections. While the wording of Objective 1.2.4 on improved performance characteristics which includes "safety" appears commendable, it is disconcerting to see this objective omitted from the Measurable Goal Indicators in Table 1, which, given the way the Plan is constructed, may be the only actions given a high enough priority that they will actually be monitored and achieved. We would like to see Objective 1.2.4 reflected in the indicators, and we would like to see consistence reference in these three Goals sections to the need for new or expanded programs to incorporate *safer* vaccine profiles, not just *safe* ones. We would also like to see recognition of the need to have adequate evidence on risk for existing and new vaccines in order to properly analyze cost, benefit, and risk for licensing and recommendation purposes.

Taken as a whole, Goals 1, 4, and 5 give the message that the current standards for safety, outside of delivery technologies, are adequate. The tone of this section makes it clear that

those who are now guiding the vaccine enterprise, including the authors of the draft NVP, find it psychologically difficult to balance safety needs with those of vaccine promotion. Their view is that as long as benefits strongly outweigh risks, the program is successful as is, the current safety profile is basically fine, and fundamental reform is unnecessary. Their view is a compelling reason for removing safety oversight from those whose primary interest and responsibility are to promote vaccines.

Comments on Goal 2: Safety is primarily covered in Goal 2 of the Plan: Enhance the safety of vaccines and vaccination practices. The indicators of measurable outcomes listed in Table 1 on pages 11-12 are as follows:

- *Conduct and disseminate the results of active and passive surveillance-based safety assessments for newly recommended vaccines or for vaccines with expanded recommendations:*
    - *Within 1 year of publication in CDC's Morbidity and Mortality Weekly Report of new or revised ACIP recommendations.*
    - *Within 1 year after X million doses have been distributed.*
- *Develop and disseminate plans for further investigation, if any, of newly detected AEFI signals and the rationale for those plans within X months of signal detection.*
- *By X year, X % of infants, children, adolescents, adults, and pregnant women will be under active surveillance for AEFIs.*
- *Conduct research to explore host factors and biological mechanisms associated with serious AEFIs and annually report results to the Assistant Secretary for Health, vaccine advisory committees, vaccine policy makers and other stakeholders.*

These outcomes are important, and we support the objectives assigned to each. However, both outcomes and objectives are extremely limited in scope and inadequate to address the recognized gaps in vaccine safety science. Our input in subsequent sections of this document describes additional activities and, more importantly, fundamental structural reforms needed to improve the safety profile of vaccines. We ask that these recommendations be incorporated into the final NVP.

Comments on Goal 3: We are also concerned with Goal 3: Support informed vaccine decision-making by the public, providers, and policy-makers. This goal as framed in the draft NVP concerns communication of risks/benefits of vaccinations to key stakeholders, including patients/parents and physicians. We support the Measurable Indicators of Goal 3 which are as follows (from Table 1):

- *Enhance communication with stakeholders and the public to more rapidly inform them (within _X_ days) about urgent and high-priority vaccine and vaccine-preventable disease issues (e.g., outbreaks, supply shortages, vaccine safety concerns).*
- *__X__ % of the public will report that they are satisfied with how their health care provider answers their questions about the benefits and risks of vaccines by Y (year).*

- *__X__% of the public will report they have access to information which allows them to make informed vaccination decisions for themselves or their children by Y (year).*
- *__X__% of health care providers will report that they have access to accurate and complete information about vaccine benefits and risks and are able to adequately answer questions of parents and patients by Y (year).*
- *__X__ % of key decision- and policy-makers will report they have access to vaccine benefits, risks, and costs to make informed decisions about vaccine policy by Y (year).*
- *By Y (year) all health professional schools and training programs will include vaccine and vaccine-preventable disease content in their curricula, and assess students' and trainees' knowledge.*
- *By Y (year) all relevant health professional certifying examinations will include vaccine and vaccine-preventable disease questions.*

We support these goals and the objectives assigned to each as they pertain to communication and education, assuming that risks, benefits, and costs are appropriately determined and objectively presented to the target audience as described in subsequent sections of our document. However, the goals, objectives, and indicators are again insufficient, for two reasons. First and foremost, this Goal avoids any mention of informed consent; communication goals must be supportive of informed consent, an essential element of any serious medical intervention. Second, Goal 3 as written is slanted toward convincing the public that the vaccine program is good for them rather than providing unbiased, neutral information that will allow the public and medical providers to make decisions for themselves. The Goal is overly concerned with making sure the public accepts an expanded program, rather than being concerned with providing the information needed to make healthy choices. Examples are Objectives 3.1.5 and 3.4, which focus on bolstering communications to underimmunized groups, while comparable objectives are absent that would help groups who might be more susceptible to vaccine adverse reactions by providing the information these groups need to understand their increased risk profile. Subsequent sections of our public input provide recommendations for additional components of Goal 3 which should be included in the final NVP.

Comments on The Introduction: As America embarks on comprehensive healthcare reform, we share a sense of hope that our public health system can finally serve the most pressing needs of children and families in the 21st Century. Yet as NVPO embarks on a future looking NVP, we see the Plan framed not to promote the health of children and families above all, but to promote vaccination. These two goals may or may always be aligned. The "Purpose, Perspective, and Scope" section of the Plan states:

> *The purpose of the updated National Vaccine Plan is to promote achievement of the National Vaccine Program mission to prevent infectious diseases and reduce adverse reactions to vaccines by providing strategic direction and promoting coordinated implementation by vaccine and immunization enterprise stakeholders.*

Vaccine promotion should be subjugated to overall health goals and the purpose or mission of the NVP should reflect this prioritization. We elaborate more on this concept below under "A Broader Look at Reform".

We agree that the NVP should be national and not Federal in scope, and extended globally. A focus on prophylactic vaccines that counter infectious diseases is proper. We support quantifiable, measurable outcomes for specific targets, not processes or aspirations, and ask that the list of milestones be broadened to encompass fundamental reform on how safety activities are undertaken and funded by the Federal government as described on subsequent sections.

A 10-year horizon with a 5-year correction review is reasonable. We feel that a less intensive annual review to ensure accountability and allow for minor revisions would be beneficial. Additionally, the vision as written in the draft Plan is that the outcomes specified by the NVP will be executed through an Implementation Plan created by the Federal agencies responsible for immunization activities. However, since we are asking in the Governance section following for a new agency or commission to be established which would have primary responsibility for safety activities and that is independent of existing agencies, we recommend that Congress and the White House be involved in reviewing the NVP and its implementation plan, not just the NVPO and the other agencies currently involved in vaccine activities.

Finally, we ask that the Implementation Plan be described in detail as it is currently too general and anemic. The details should be opened for public comment prior to finalization. Meetings held to create and evaluate the NVP and its implementation should be open and accessible to the public. Public advocates who focus on vaccine safety should be included and welcomed in these activities and such representatives should be specified as equal members of the vaccine and immunization enterprise stakeholders group, which right now is almost exclusively comprised of those who focus on promotion.

Safety Must Be a Central Theme Within the NVP

Congress imposed an express mandate for safer vaccines in amendments to the Public Health Service Act, 42 U.S.C. 300aa-27, by the National Childhood Vaccine Injury Act. Safety should be an equally valued partner to the National Vaccine Plan components which focus on new vaccine development and extending vaccine programs to the population, communications, supply, and global impact. A Safety First program would fully support science, ethics, law, legal remedies, medicine, public trust, policy, business practice, and funding priorities.

The continued societal benefits of mass immunization depend on an aggressive Safety First system centered on sound science that identifies and minimizes acute and chronic adverse events; respects ethical informed consent and individual autonomy; is independent of vaccine promotion; has meaningful oversight; is accountable, transparent, and honest; and has an adequate safety net to take care of and fully compensate those harmed by vaccines.

As is recognized by the leadership of the vaccine safety enterprise, yet sadly not addressed in practice, features of our mass vaccination program demand a Safety First

agenda at least as or even more stringent that that expected for other controlled medical products with comparable potency.

- Vaccine benefits come with a cost of a range of adverse effects. However the magnitude of the benefits to society attributed to vaccines dwarfs the recognized adverse effects. The imbalance has stifled the moral, legal, and ethical duty to the individual to minimize harm from vaccines. The imbalance inevitably leads to pressure to ignore, trivialize, or accept as unavoidable any adverse effects by public health and medical practitioners. A strong Safety First program will always be needed to counterbalance this pressure.
- Unless disease rates are high, there is tension between the needs of the many, embodied in the concept of preventing a resurgence in disease through herd immunity, and the needs of the individual, who bears the burden of risk from adverse effects. As a matter of law and ethics, competing obligations must be resolved in the favor of the individual. Compensation by society to the individual for injury, no matter how generous, cannot substitute for good health. Reducing vaccine adverse effects so that fewer individuals experience injury is an ethical remedy and is an obligation independent of the benefits from reducing the burden of infectious disease.
- The public also expects a higher degree of safety when large numbers of individuals are exposed to a vaccine and when universal use is essentially mandated through school/day-care entry rules or employment terms. A higher safety standard is also expected by the public from prophylactic vaccines given to healthy children and adults to avoid the low possibility of disease than from other medical interventions given to treat a disease or injury already acquired. The lower tolerance for vaccine risk leads to a need to investigate – and eliminate – the causes of adverse outcomes from vaccines more so than from other medical products.
- Most vaccine adverse effects are considered rare relative to the doses administered and complex in that the same outcome may arise from both vaccine and non-vaccine factors or the outcome may be caused by an interaction of factors of which vaccines are one. Yet the public is very concerned over rare and complex AE's as shown by the response to new safety evidence on anti-psychotics and NSAIDs. Such attitudes are likely to extend to vaccines. A strong safety program would satisfy the public's expectations for exhaustive safety data irrespective of event rarity or extenuating factors.
- Public acceptance of risk erodes over time as diseases targeted with vaccines are reduced or eliminated, leaving distant memories of harm. Meanwhile, present-day reports of vaccine adverse reactions make more alarming impressions. Newer vaccines tend to be directed at low prevalence or less serious diseases with a less pronounced benefit/risk ratio, making parents and patients more likely to scrutinize the risk side of the equation. New vaccine approvals have added many more antigens to the schedule, and concerns will naturally increase over the safety of multiple shots given in a visit, multiple antigens in a single shot, and multiple antigens given in a short window of time during early development.
- More healthcare conscious parents and patients can use the internet to find out quickly whether the safety a vaccine or of the complete schedule has been evaluated and what the state of the science is. They can find out what types of cases have been compensated in Vaccine Court, who is paying the investigators of official studies, and

> whether the government has conducted the research they say they have. Erroneous or uncertain association between a vaccine and an adverse event can quickly undermine public confidence. However, denial of association without adequate and unbiased evidence also erodes confidence. The government's response to safety must be robust enough to meet the expectations of the savvy consumer. In fact, the high coverage rates needed to meet herd immunity thresholds mean that, absent the use of governmental coercive powers, safety concerns must be addressed in a way that satisfies nearly everyone, a tall hurdle and certainly one that necessitates a broad and participatory safety program.

Uptake could rapidly decline because of the growing asymmetry of risk perception coupled with current gaps in science knowledge that are exacerbating doubt. Should the public perceive that a substantial burden of chronic adverse reactions is or was avoidable, a catastrophic drop in uptake is a real possibility, along with demands for accountability and adverse economic and political consequences for industry, medicine, and public health. The public has been relatively tolerant of safety breaches in the past, including the Cutter Incident, SV40 contamination, atypical measles syndrome, whole cell pertussis brain damage, the withdrawal of RotaShield, and the excessive cumulative mercury content of infant vaccines. Surveys show that uptake has remained high. The crucial distinction is one of perception. Public intolerance can be expected – indeed, a softening of public confidence and trust and a rise in parent questioning of pediatricians are already detectable - if deepening safety concerns are met with inaction, deliberate ignorance and obstructionism. The public looks to the Federal government to ensure the safety of medical products; as the government's strategic plan for vaccines, the NVP must ensure that the public's expectations for vaccine safety are met.

The Importance of Fundamental Safety Reform

In an era of comprehensive healthcare reform, a forward-looking public health practice would not value vaccines as a benefit in and of themselves. Rather, it would embrace a mission of *securing health outcomes* for children and adults first and foremost, and it would value vaccines only to the extent that they advanced this mission. We feel the NVP should reflect this hierarchy and the purpose of the NVP as written on page 17 be revised as follows:

> The purpose of the updated National Vaccine Plan is to promote achievement of the National Vaccine Program mission to prevent infectious diseases and reduce adverse reactions to vaccines and to promote the overall health of Americans by ensuring that the National Vaccine Program serves the inclusive healthcare needs of Americans. The National Vaccine Plan purpose will be achieved by providing strategic direction and promoting coordinated implementation by vaccine and immunization enterprise stakeholders and by coordinating its goals with other entities involved in non-vaccine related health promotion activities.

The NVP should not operate in isolation from other important healthcare initiatives but be part of a forward-looking public healthcare practice that puts vaccine benefits, risks, and costs in a broader context. This practice would embrace a commitment to a *total health perspective*, including chronic as well as infectious disease, developmental disability as well as episodic illness and quality of life as well as the absence of disease. Such a perspective would recognize the crisis of the *chronic disease epidemics* among children, including autism, learning disabilities and other neuro-developmental disorders as well as asthma, food allergy and juvenile-onset diabetes. This perspective would not allow vaccine promotion to proceed at the expense of supporting science and treatments of these conditions. A reformed system would also adopt:

- A vaccine policy that treats all citizens including parents as intelligent participants in the health choices they make for themselves, their children and their communities and requires true *informed consent* and *real choice* for participation in vaccine programs;
- An operating philosophy that sets a goal of *zero vaccine adverse events* and treats each event respectfully, or even better, as a resource for diagnosis and prevention of future vaccine adverse events;
- A governance model for vaccine policy-making based on *true public accountability*, characterized by public inclusion, openness to scientific criticism and a willingness to accept past shortfalls as an opportunity for learning, growth and change;
- A governance and operational model that truly separates safety from promotion, at all levels; and
- A commitment to securing the science, scientific practices, and science communication practices that meet modern standards for patient safety, comparative effectiveness and evidence-based healthcare decision-making.

We believe that this positive focus is notably absent in public health policy and practice today among the vaccine enterprise leadership. Of concern, the negative policies and practices of the past are in danger of being carried forward under the draft Plan unless it incorporates comprehensive and fundamental reform. Specifically, we see an historical approach to vaccine policy and practice still embedded or not confronted in the Draft NVP that is fixated on:

- A mission of fighting a war on disease, irrespective of secondary and tertiary consequences or of the inevitable casualties of the war;
- A goal of preventing every single case of “vaccine-preventable disease” worldwide, regardless of cost and achievability, even if such actions divert resources from other pressing needs or escalate the number of injuries from adverse events;
- A commitment to an unprecedented expansion in the childhood vaccine program, with inadequate, if any, consideration given to the cumulative and interaction effects of this strategy;
- A communications strategy that fits the definition of propaganda: hyping the risk of infectious disease through fear, hyperbole and incomplete information; zealously denying both the possibility and extent of plausible adverse reactions such as brain damage leading to autism; and selectively presenting the evidence in order to herd the public into compliance rather than to inform;

- An agenda that prizes product expansion and compliance so highly that advancements in patient safety practices, already being applied to a broad range of healthcare fields, are largely shut out of the vaccine enterprise;
- An operating ethos in vaccine safety management of utilitarianism, one that allows for "acceptable losses", an approach that places "safety last" in funding priorities;
- A pattern of governance in which many decision-makers have direct financial and/or career conflicts of interest that produce biases to program expansion and the defense of past policy decisions.

The present state of vaccine policy and practice is contrary to science, ethics, and law. Public acceptance of vaccination is declining and will continue to be in jeopardy without a meaningful Federal commitment to a Safety First scientific research program, safety net, and governance structure. A description of the details of these three components of the Safety First agenda forms the remaining sections of this document.

Vaccine Safety Science Enhancements

a. Pre-licensure safety research

An adequate vaccine safety research plan must emphasize pre-licensure activities to the same degree as post-licensure ones. Leaving gaps in safety knowledge during the pre-licensure phase means post-licensure vaccine recipients serve as guinea pigs for insufficiently tested products, with potential repercussions on health. Patients, healthcare providers, and policy-makers cannot weigh risks with benefits without comprehensive safety data which is reported fully and fairly. Existing pre-licensure vaccine safety research practices are inadequate when analysed according to standards now expected by the patient safety movement. For example, several Cochrane systematic reviews have described significant failings.

> *Licensed vaccines for rotavirus*: "Main Results: …Results on mortality and safety of the vaccines were scarce and incomplete."[1]
>
> *MMR vaccine*: "Authors' conclusions: The design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate." [2]
>
> *Licensed influenza vaccines*: Plain Language Summary: …It was not possible to analyse the safety of vaccines from the studies due to the lack of standardisation in the information given but very little information was found on the safety of inactivated vaccines, the most commonly used vaccine, in young children. [3]

As a start, we recommend that pre-licensure vaccine research adhere to the same best practices as those in place or being put in place for drugs and devices. Comprehensive registry of clinical trials is underway and vaccine trials should likewise be registered. The National Library of Medicine will likely develop uniform reporting requirements as a component of registry. Standard reporting enables independent researchers to pool multiple trials for analysis. Serious safety concerns from widely used drugs often only

emerge from such meta-analyses. Standard reporting also provides the public, practitioners, and policy-makers with easily understood benchmarks that can be readily learned, accessed and applied. Examples of how pre-licensure vaccine trials should adhere to best practices are list below.

- Stage 1 and 2 research should be made available and accessible to the scientific community and the public. The public needs to be confident that safety signals from early stages are incorporated into stage 3 studies. Moreover, efficacy or safety data from a phase I or II trial could ultimately wind up being significant when pooled with larger phase III trials, especially when the total pooled sample is small.
- Stage 1 and 2 trials should include study of the effects of the new vaccine as part of a larger vaccination regimen and not just in isolation. Such studies should include humans and animals.
- Stage 3 trials are increasingly conducted overseas. Registration and results reporting of international trials should be required.
- Vaccine trials are generally designed poorly from a safety perspective.
    - Virtually all trials do not have a true placebo group. The control arm may be another vaccine which can also be reactogenic or a saline solution with an adjuvant, preservative or stabilizers. Any trial should have a placebo arm using an inert substance, otherwise the adverse event comparisons will be inaccurate.
    - Study groups are healthy, although the vaccine is recommended for the unhealthy as well. Best practices inform us that gold standard RCTs are only applicable to the conditions of the RCT. Either late stage trials should be expanded to include a subset of unhealthy subjects or vaccine recommendations should be limited to healthy people.
    - It is now generally recognized that subgroups may have a higher risk for an adverse reaction. These subgroups are hard to identify and therefore hard to study pre-licensure. Still progress could be made by studying pre-licensure those who might have had a reaction to other vaccines or who showed a reaction during licensing trials. As more basic science is conducted on vaccines, potentially susceptible subgroups should be included in licensing trials.
    - Phase III studies are powered to detect treatment effects. Sample sizes are too small to detect adverse effects that occur less frequently, generally at less than 1 in 1000. Studies should have larger sample sizes to detect less frequent outcomes if the vaccine will be recommended for mass use.
    - The follow up period in trials is too short to pick up long term adverse effects. Only acute events are detected. Follow up should extend over many years, for example, at least 4 years, when infants and young children are the target group.
    - Doctors overseeing the clinical trials are allowed to decide when an ailment occurring after vaccination is an “adverse effect” that merits reporting to the study team. (See, for example, the varicella vaccine trial descriptions.) Reportable event definitions should be established ahead of time and reporting should be mandatory.
- Reporting of vaccine study findings reflect the same problems as many drug trials. Standardized reporting using objective criteria should be put into place now to meet future needs for comparative healthcare effectiveness and assessment of risk/benefit for individual patients.

- Mismatched framing: harm is generally presented as absolute risk, or percent of patients in the study who experienced the reaction, whereas benefit is generally reported as relative risk, or the percent protected from future disease, that is, sufficient seroconversion. Both harm and benefit should be presented the same, in both relative and absolute risk terms.
- Attributable risk (AR) and population attributable risk (PAR) should be reported for both risk of adverse effects from the vaccine and risk of morbidity or mortality for the vaccine-preventable disease. These values should be given for the population for which the approved vaccine is intended or recommended (PAR) and framed, to the extent possible, to mirror the profile of the individual to whom the vaccine will be given (AR).
- Calculations of vaccine benefits from reduction in the infectious disease (AR, PAR) should consider secular trends in infectious disease reduction occurring independently of vaccination, that is, not attributable to the vaccine, for example, implementation of hygienic practices or use of more effective antivirals. Calculations should also utilize time frames that correspond to the targeted infectious disease cycle and not just peak incidence or peak morbidity/mortality years from historical records.
- Calculation of risk from adverse effects (AR, PAR) should be reported as a composite risk measure, grouping them by severity, in addition to reporting the risk of any given one individually. The rational is that a patient is interested in knowing the risk of being harmed at all, as well as the risk of having a particular reaction. In addition, a narrowly defined AE may not reach statistical significance, but combined AE's might. For example, the incidence of a single severe reaction like a seizure might be less than 0.1%, but the incidence of all severe reactions cumulatively (seizures, ataxia, Stevens-Johnsons syndrome, etc.) may total 1% and significantly exceed placebo outcomes or background rates.
- The number needed to treat (NNT) is an important calculation for assessing risk/benefit and cost/benefit. Certainly the NTT for vaccines intended for mass use, especially those producing short-term immunity requiring boosters or inducing pathogen strain replacement requiring later administration of new antigens, is quite high since they rely on herd immunity for effectiveness. Standard, unbiased methods for calculating NNT, ideally based on actual clinical practice and not models, should be created for vaccines. NNT should be routinely reported with clinical trial results and refined/updated on a regular basis post-licensure as real world effectiveness over the long-term is monitored.

- The vaccine formulation studied should be the same as the one that is actually produced post-licensure.

To uphold public confidence and ensure that healthcare providers have all pertinent information, the FDA should remove the "confidential commercial information" exclusion for vaccines which are mandated by ACIP and paid for by the Vaccines for Children Program. Public health interests should trump private commercial interests. The exclusion covers the trial results that have already been submitted to the FDA but are never publicly disclosed. Going forward, the FDA must publish results from the trials for approved drugs, biologics and devices, but only after having received at least three freedom of information act requests. The FDA is prohibited from publishing any trial

results for drugs, biologics and devices that fail to pass the agency's safety and efficacy requirements, which is about half of all applications. As Alastair Wood, managing director of Symphony Capital and a Professor of Medicine at Cornell University's Weill Medical College in New York, wrote recently in the *New England Journal of Medicine*:

> "The argument that such data must be withheld so that potential competitors do not benefit runs counter to the principles of ethical human research, which require that risks to human volunteers be minimized and that human participation in research leads to generalizable knowledge."

We agree with this statement and hope such recommendations are incorporated in the final NVP.

b. Post-licensure research

Stage IV trials conducted by manufacturers, requested by FDA as a condition of licensure, should adhere to the same practices as described for pre-licensure trials, as above. Harmonization of stage IV methodologies and reporting would allow phase IV safety data to be pooled with pre-licensure data, in order to boost analytic power. A mechanism should be put in place by FDA for the public to track whether the requested post-approval studies have been launched and the status of the project.

Whether drugs, devices, or biologics, post-licensure safety monitoring by industry is inadequate. The main source of post-approval safety information is government-run surveillance which, by monitoring health outcomes in the real world, often detects unforeseen adverse effects. Yet the government's mainstays for vaccine surveillance, the VSD and VAERS, plus limited clinical investigation through the CISA Network, are weak, lack transparency, and are essentially closed to the scientific community. Many of the problems with these activities mirror those identified for FDA safety surveillance efforts in general, that is, are not unique to vaccine safety. As drug and device surveillance practices are improved under the new Administration, we ask that equivalent improvements be applied to vaccines and that these recommendations be spelled out in the NVP.

VAERS: Use of VAERS by independent scientific investigators is critical to maintain public confidence. Use of VAERS by scientists is impeded due to arbitrary administrative glitches and willful suppression of vital data.

- Lot numbers are often missing. Other key record information is inconsistently recorded. Data is modified without explanation, for example, Gardasil deaths have been entered and then removed. When a symptom coding and categorization scheme called MedDRA was initiated, terminology was altered (for example, simple terms like 'edema' started showing up as 'oedema') and no crosswalk from the old codes to the new codes was provided. Simple illogical entries are easily found. For example, the right hand column in one VAERS report had 'No' marked to "Life threatening illness?" and then had 'Yes' marked to "Died?".
- VAERS reporting lags the event, delaying or clouding signal detection. Findings can change depending on whether data is run by date of vaccination or the date the report

is submitted. Excessive variability is observed from month-to-month and year-to-year.
- VAERS does not disclose the critical denominator of how many doses of a vaccine was distributed, making it difficult to determine if an increase in reported events is due to a safety issue or to distribution of more doses. The government's preference for protecting proprietary manufacturers' information at the expense of public knowledge and valid scientific investigation is untenable.

VAERS weaknesses include incomplete reporting and lack of clinical data such as biospecimens, DNA, and medical histories.

- VAERS should be transformed into an active surveillance system through mandatory reporting by providers with penalties, and through enhanced communications to providers and patients of the reporting process. This is especially important as vaccination sites expand to alternative settings and the schedule becomes more complex.
- VAERS could incorporate clinical data, and in fact the ISO draft agenda specifies obtaining clinical data of VAERS cases. Clinical data can help elucidate mechanisms and characterize the severity of the event.
- VAERS should be pro-active in reporting detected adverse effects back to providers, so they can be better prepared to identify and treat such reactions in their patients.

VSD: Given its importance, the VSD should be upgraded from "administrative" to research quality. HMO medical records are often inaccurate because they are a by-product of care rather than a scientific research effort. A large proportion of subjects are lost for follow up on long-term studies because they leave the HMO and are no longer tracked.

Important subgroups like unvaccinated, lightly vaccinated, overvaccinated and "catch-up" children are underrepresented; their low sample sizes mean they cannot be studied, a critical omission for a vaccine safety effort. The CDC should undertake outreach efforts to include healthcare sites which serve families who may choose to vaccinate differently or not vaccinate. CDC could also instruct the HMOs to provide a vaccine exemption status check off box for enrollees, rather than assume, as in the past, that no polio shot in infancy means that the child was vaccinated elsewhere. CDC outreach should target families who may lack consistent access to healthcare and thus may of necessity vaccinate differently. Underserved children may only see a provider when they are sick and the provider cannot access their vaccination history. These children may receive many vaccines, some unnecessary, on one day when ill.

The VSD could be enhanced in other ways. Better linkage between mother and child medical records would allow analysis of maternal exposures along with infant vaccinations. Better linkage with VAERS might foster mechanisms to investigate AEFIs that do not result in a formal clinic or hospital visit. More subtle conditions and developmental conditions, like autism, speech problems, and learning issues, are not tracked well by the VSD HMOs. For example, rates of autism in VSD analyses do not match those from other more rigorous sources. HMOs who are participating in the VSD

should be required to follow a standard plan for tracking developmental outcomes and other health outcomes of interest that may not reach severity for a clinical diagnosis or for which the diagnosis is made by a specialist outside the HMO.

VSD data should be under direct government control and not the HMO's. The numerous HMOs, set up as intermediaries and each with its own rules, add an unnecessary and cumbersome bureaucratic layer and significantly hamper access to the data by independent researchers. With respect to vaccine safety, HMOs can, and in some cases do, provide important information resources for safety management. Given the value of their patient data, HMOs have an interest in maintaining control over their private databases. Pooled databases like the VSD provide information resources of extraordinary potential societal value; yet by increasing the transparency around health outcomes across different participating HMOs, information sharing also threatens the autonomy of these organizations. The public interest lies clearly in full and prompt reporting of health outcomes, especially as they relate to vaccine safety, but HMOs have resisted the expansion of public health claims on their data resources. They typically fall back on claims of patient confidentiality to restrict outside access, but these claims are rarely in the interests of their patients, instead they are largely a mechanism to retain autonomy and control. As a consequence, resources for vaccine safety reporting are highly restricted, non-standardized, inaccessible and unreliable for assessing health outcomes. We would like to see the VSD contract with the HMOs revised to eliminate many of the egregious proprietary claims of the HMOs.

The VSD and VAERS rely heavily on estimated "background rates" to detect AE's. The methodology for assessing these rates is too vague. As with autism prevalence, prevalence/incidence of other diseases/conditions is generally not accurate and masks true increases in conditions post-vaccination. Attributable risk calculations are not possible to produce without accurate incidence rates. Methods to improve background rates must be developed.

Analyses in science journals using VSD and VAERS often reflect the same deficiencies in reporting noted above in pre-licensure studies and for typical drug trials. These include mismatched framing, highlighting of relative risk versus absolute risk, absence of AR and PAR, biased reporting of infectious disease risks (peak years rather than cycle averages), reporting of individual rather than composite AEs, and so forth. Such reporting standards should be requested by the NVP.

c. Basic science on vaccination and the overall vaccination program

Significant gaps exist in basic science on response to vaccination and how this might lead to an adverse reaction; in fact the state of the science could be described a rudimentary. To fill the gaps, this science must be fully supported financially, not done "on the cheap". Government commitment to such endeavors will go a long way to restore public trust in vaccination. This body of science must consist of in vitro studies (biochemical, genetic, systems biology and other cell-based experiments); animal models including non-human primates; human studies including clinical investigations and epidemiology which may be observational and retrospective as well as prospective and that employ statistical

controls as well as experimental designs; and an extensive bioinformatics and biospecimen infrastructure.

As the vaccine program has expanded, and as toxiciological and immunological science on the effects of multiple exposures on a developing organism becomes more sophisticated, vaccine safety considerations have grown more complex and urgent. In addition to the ongoing concern over acute single vaccine adverse events, we need to recognize new exposure risks, either from a cumulative effect of vaccine ingredients or from the unintended consequence of interactions between vaccines and other environmental exposures on the developing immune, endocrine, metabolic and nervous systems. Since each vaccine is added to a pre-existing regimen, the science done to date cannot tell what the total regimen cumulatively is doing, particularly against a background of increasing environmental exposures and changes to modern diets.

- Vaccine mercury exposure provides an example of the cumulative risk problem. Exposing the developing brain to mercury was never a good idea, but the introduction of two new vaccines in the early 1990s (not to mention the increasing practice of antenatal Rho D immunization), coupled with the drive for earlier, on-time immunization, more than tripled the earliest exposure rates, effectively compounding acknowledged mercury risks to pregnant mothers from seafood consumption and dental amalgams. When some mercury exposure is bad, then more is unquestionably worse, yet new fetal and childhood mercury exposures are continuing via influenza vaccines.
- The effect of higher and repeated doses of aluminum has also not been studied. A number of published papers suggest an adverse effect profile of injected aluminum, yet the cumulative dose of aluminum has steadily increased.
- Science is increasingly showing that many pollutants act on the same biological pathways and can result in similar adverse outcomes. We need to understand if vaccine ingredients operate through these same mechanisms, and if vaccines might exacerbate the effects of background pollutants or act as adverse event triggers to an already compromised individual.
- More complex, but no less concerning, is the issue of interactions. We simply do not know what the risks of the 30+ antigens and 12+ disease exposures of the infant schedule might be when combined together. In the face of the escalation in recommended doses, common sense would suggest a testing discipline involving more than each new vaccine, or even combination vaccine, on its own, but of the old schedule versus the new strategy *in their entirety*. The full vaccination schedule fits the definition of a complex treatment regimen, and complex medical regimens are generally tested for safety and effectiveness.

It is unethical NOT to do these studies. Many vaccine-concerned parents - and most likely a number of medical ethicists - view a state-mandated vaccination program that lacks even basic scientific evaluation of the combined and potential interactive effects (let alone identifies those at higher risk of AE so that their decisions could be appropriately informed) to be at best an unethical practice.

The "Vaccine Safety Continuum" recognizes the need for animal and clinical studies in pursuit of safety and the need to study immunology and microbiology. Yet application of this science to access vaccine safety has been minimal. Recommendations to address the gaps in basic vaccine safety science are as follows:

- Even a slight adverse reaction from one vaccine might indicate a susceptible person. These would be fruitful subgroups to study extensively, and might include cases of autism where regression was noted as an acute decline immediately after vaccination.
- Basic information on mechanisms and differential response to vaccinations due to genetics or other individual factors like health status, age, or exposure to other toxins, is needed for early medical treatment subsequent to vaccine-injury and to discover other possible effective treatments for adverse reactions from vaccination which could decrease morbidity and progression to severe life-long adverse conditions.
- We know that genetic variations exist that cause adverse reactions to specific foods, medications, or anesthetic agents. It is legitimate to ask whether a similar situation may exist for vaccines. Some studies have linked specific mutations to adverse reactions to vaccines (sodium channels) but certainly additional plausible gene differences must be explored, for example, whether subpopulations unable to remove metals from the body as fast as others react poorly to thimerosal or aluminum, whether those prone to demyelinating autoimmune disease are prone to vaccine adverse reactions, or whether those with an underlying mitochondrial disorder are at increased risk due to vaccine-associated fever. Significant effort is required to identify genetic susceptibilities and biomarkers.
- Biological and genetic research could include profiling of those having an adverse reaction compared to controls and of unvaccinated compared to vaccinated individuals. Profiles might include protein microarrays to identify cytokine profiles; SNP, CNV, and gene expression profiles (some of this work has already started at the Vanderbilt genetics center and CISAs); and microarrays of genes expression involved in immune response. Beyond identifying single biomakers, clinical studies should be started right away which employ a complete work up of genetics, biomarkers, medical history, MRIs, and exposure history of those who had an AEFI, initiated right after the AEFI occurred.
- Variability in the response to vaccination might relate to timing in relation to development, that is, vaccination outside of vulnerable windows may reduce adverse reactions. This issue should be studied and could impact decisions on the schedule.
- Variability in vaccination response may also be due to prior exposure history, including exposures prenatally. For example, exposure to methylmercury in mice in utero results in ongoing oxidative stress that persists into adulthood, even after mercury clears from the body.[4] Such persistent effects could create a susceptible individual more likely to have an adverse response to a vaccine. These interaction effects should be studied.
- Many adverse events are rare and require large samples to detect. Investment in identifying intermediate responses which do not result in a detectible adverse reactions, akin to testing for seroconversion rather than primary disease prevention, would be fruitful. Intermediates might include biomarker changes or gene expression changes, in animals as well as humans. Likewise, some outcomes are not evident until many years after vaccination and may result from multiple etiologies but are

characterized by the presence of more defined, precipitating physiological conditions. An example would be an outcome of autism which is behaviorally defined and was precipitated by mitochondrial collapse shortly after vaccination. Studying the proximal and defined physiological conditions might be more fruitful than studying with the long-term, complex outcomes.

- Vaccine ingredients - stabilizers, adjuvants, preservatives, inactivators, growth media - should be subject to their own safety tests. Such tests should involve standard toxicological testing with a 100-fold safety factor using cell culture and animals, with substances tested individually and synergistically. Any currently used ingredients that are "grandfathered in" should also be tested. As toxicity testing techniques improve, they should be applied to vaccines.
- Some people wonder if vaccines "weaken the immune system". This is a non-specific statement but there are valid health questions as to the effects of vaccination on general immune system function. Examples of areas to explore are viral interference after vaccination, the duration of wild type versus vaccine immunity, viral persistence after vaccination, alterations in mast cell activation, enhanced susceptibility to later immune triggers due to "hygiene hypothesis" considerations, and so forth. A related concept is the research showing that environmental pollutants such as mercury may alter the immune response to vaccination (for example, work by Ellen Silbergeld), and this area needs more investigation.
- Research on interactions between vaccines and other medications is limited and should be expanded.
- Some information exists that certain dietary deficiencies can hamper the immune response to vaccines or increase adverse event rates, for example, vitamin A deficiency and measles vaccine. Other deficiencies may well exist, creating a more susceptible individual, and research in this area could lead to prevention of adverse reactions.
- Vaccines are being recommended for pregnant women but few studies exist on the effects on the fetus or how to even study this.
- Studies should be initiated on the long term effects of early vaccination throughout the lifespan. New research shows that many diseases of aging, like Parkinsons and schizophrenia (see Ezra Susser's work on famines), had their onset during the prenatal period or infancy and only manifest later in life. The Paul Patterson schizophrenia research shows that maternal response to influenza during pregnancy increases the risk of schizophrenia later in life. These effects are never investigated in vaccine safety studies. They require longitudinal human studies as well as animal studies where effects can be picked up in a shorter time period. There is also a need to look at intergenerational effects of vaccination, for example, do vaccines cause epigenetic changes that alter the immune response in later generations.
- Older vaccines have not been adequately tested using newer standards and techniques. The government agencies should re-examine the safety profiles of these vaccines, including those for diphtheria, tetanus, measles, mumps, and rubella.

Above all, an expedited comprehensive research program on total health outcomes comparing vaccinated and unvaccinated groups, which would include humans, animals, and cell culture studies, must be launched to understand mechanisms and human health outcomes. These studies should begin immediately, employ a variety of study designs

and populations, be conducted by unbiased scientists, be subjected to transparency, and involve stakeholders in all phases. Some of these studies may employ prospective RCTs, but many would employ other designs. In vitro studies could be launched immediately and completed quickly. Animal studies could also be launched and completed in an intermediate timeframe. Vaccination history should include prenatal as well as postnatal vaccines.

- Deconstructing and identifying the basic mechanisms by which vaccine-induced injury occurs is the single most important research program that we can support. A rigorous safety science program would entail an in-depth study on the basic biological mechanisms by which vaccines (antigens and components) cause immune, metabolic and neurological changes. This critical information is needed to bridge the gap between vaccination and pathophysiology being associated with vaccination.
- While animal and human immune systems differ and no animal is a perfect model, animals are routinely used for safety research and especially for toxicological studies. Different species are better suited for some studies than others. Basic mechanistic data and signals of potential harms from vaccines, vaccine ingredients, and various vaccine combinations and schedules can be obtained quickly, ethically and at lower cost. The idea that animals cannot provide relevant data for human response to vaccines is unwarranted and suggests an excuse for not moving forward on this important area of research.
- Another reason being advanced for not conducting a study of unvaccinated groups is that these groups are to difficult to find, or they differ substantially from the vaccinated in relevant ways, like genetics, diet, behavior, or health status. However, the number of unvaccinated, lightly vaccinated, or alternatively vaccinated is growing, and many are typical "suburban" families who are actively choosing not to follow the recommended schedule. Finding these families for enrollment is doable; they can be found through integrative health providers, midwife practices, homeschool organizations, Waldorf Schools, in certain geographic areas, and even through random, rapid screening telephone surveys.
- Another excuse being used to avoid comprehensive investigation of vaccine safety is that the unvaccinated enjoy herd immunity, so a study of total health outcomes would miss infectious disease morbidity these individuals would experience if vaccination coverage were low. However, such outcomes can be modeled and factored into the analysis of any such study.

Safety issues related to vaccine manufacturing or delivery practices need more research. More obvious topics are disease from needle sticks, non-sterile products, and vaccine failures. Additionally, clinicians do not have time to assess and collect needed information on a potential AEFI. Patient/parent signals are dismissed and the child is not adequately treated or not reported to VAERS. Research on effective clinical guidelines would greatly help.

d. Building capacity on vaccine safety science

An unacceptable hidden assumption in the current approach to safety is that even an inquiry into safety, much less proof of potentially avoidable acute and chronic burdens, puts at risk the public's acceptance of vaccines. Such a strategy of "deliberate ignorance"

is self-defeating. The available evidence from the public and pediatricians is that safety concerns are on the rise, public confidence is waning, and that exemptions and alternative vaccination schedules are on the increase. In the past, lack of access to vaccination was considered among the greatest barriers to high vaccination rates. It could be argued that public concern over safety may now be the greatest impediment to achieving coverage goals. This shift argues for more resources to be devoted to safety science than has been done in the past, and for official attitudes to encourage safety inquiries by scientists.

Vaccine safety research is seen as a career killer. Scientists who try to study potential adverse events are marginalized and criticized. Their funding is cut. Government agencies need to publicly reach out to scientists and bend over backwards to show that this research is endorsed by science leaders and funders. Scientists from a variety of fields – toxicology, immunology, primatology, other animal experts – should be encouraged to incorporate vaccine safety questions. Given the current small size of the vaccine safety field, government funding agencies should support smaller scale pilot or preliminary studies on safety that will allow subsequent funding from NIH for larger grants. Most importantly, significantly more funding should be allocated to vaccine safety science. This is the best way to build the field.

Safety science needs a vastly increased budget which must be appropriated, not just authorized by Congress. Safety science will be best advanced if its activities are separated from the rest of the National Vaccine Program activities which are highly promotional and intertwined with manufacturers' interests. One reason safety has been underfunded relative to vaccine promotion is the absence of private gain for industry or scientists who make money from patents or for their labs from developing new vaccines. Safety must be a government function, yet historically the government has failed to meet its regulatory responsibilities in this arena. A separate vaccine safety agency with its own budget, priorities and practices will rectify this imbalance. (See section on Governance for recommendations on the features of this agency.)

Specific activities to enhance vaccine safety capacity should be added to the NVP and would include the following:

- More innovative studies would be facilitated by opening the CISA databanks including biospecimens, VSD data at the fully linked and patient level, and comprehensive VAERS information to outside scientists, and not just to government-approved insiders, without onerous restrictions. Standard mechanisms exist to ensure patient privacy; no valid reasons exist that preclude broad scientific access.
- Technologies supporting vaccine safety research should be applied, including database linking, data mining, and sophisticated bioinformatics.
- The government should send a signal to scientists and manufacturers that it values the development of safer practices to protect against infectious diseases. Industry is likely to respond through a more comprehensive shift to safety through process re-engineering that will result in a new generation of vaccines or other interventions that embody safety. Many parents and adult patients would like to see "green vaccines" without harsh ingredients like aluminum, mercury, synthetic adjuvants, and residue from growth media, and without the need for potentially harmful injections.

- NIH and CDC should issue more RFAs, stimulate greater interest among scientists in existing NIH/CDC RFAs on vaccine safety, and convene an expert panel to develop designs or draft RFAs which will be more successful than current efforts.
- Existing larger studies can be enhanced to encompass safety questions. For example, NHANES and the National Children's Study should include complete vaccination histories and confirmation of what vaccines were received (not just based on maternal recall), and they should oversample unvaccinated or lightly vaccinated groups through pro-active outreach recruitment efforts. With additional effort, the NCS could obtain a minimum of 2,500 non-vaccinated children.
- Some of the work needed for safety research can be conducted through existing mechanisms, for example, the VTEUs at NIAID or through NICHD which has experience overseeing vaccine studies. NICHD also has autism experience and may be a logical choice to build safety science capacity.
- Education on vaccine safety should be expanded. Vaccine risks and how to identify, report, and treat a vaccine adverse reaction should be taught in medical schools. Refresher CMEs should be offered regularly. Parents and adult patients should be given a comprehensive list of suspected adverse reactions, not just a truncated informed consent form, so they can see if an AE is happening and contact a healthcare provider.

The Value of a Strong Vaccine Safety Net

Treatment and prevention of adverse effects should form the core component of a safety program. Parents and injured adult want their or their children's health restored, not compensation, and want above all to know that scientists are trying to find answers, not just write the injury off as the downside of public health promotion. Until vaccine safety science is improved and concern remains, among the only avenues for achieving meaningful change left open to the public are civil litigation, rejection of vaccine mandates, and parents' rejection of vaccines or of the official schedule. Only through an aggressive Safety First research agenda and a truly meaningful and adequate safety system can the growing "sagebrush rebellion" against the ever expanding regimen of recommended vaccines be averted.

a. Strengthen real choice within informed consent

In an open society, we typically rely on the free choices of informed citizens as the corrective mechanism for dealing with complex trade-offs. We express our freedom in two ways, through the free market (for economic trade-offs) or free elections (for policy making). In either domain, we know from long experience that assigning decision rights to centralized state authorities can produce lasting inefficiencies and/or inappropriate concentrations of power. Checks and balances on such power are essential to prevent the abuse of power by the state and improved outcomes for society.

Vaccine programs introduce special problems in an open society. Programs for infectious disease prevention rely strongly on herd immunity. Achieving herd immunity requires widespread compliance, indeed significantly greater compliance than either free markets

or free elections require for success. Vaccination coverage rates sufficient to provide herd immunity are estimated in the 80-95% range depending on the disease. Achieving such high compliance rates in large populations demands extraordinary efforts. Compounding this difficulty, public health officials have increasingly defined success as compliance rates approaching 100%, a shift from a goal of herd immunity to elimination of disease entirely. With such aggressive targets the exercise of economic choice ("I don't want to receive that service") or the declaration of dissent ("I don't support that policy") runs in direct opposition to the interests of the bureaucracy in meeting its performance goals.

In order to reach compliance targets, vaccine program participants ask for and typically receive exemptions from normal checks and balances on state power. These exemptions are justified because the prevention of disease is seen as an area in which the interest of the collective overrides the rights of the individual. Consequently, manufacturers receive exemptions from product liability laws. Citizens face powerful sanctions if they fail to comply with state recommendations—children can be denied entry to school, parents can be declared negligent, and pediatricians can deny service to families when they choose not to vaccinate. Program managers are protected from accountability to external parties in numerous ways.

These exemptions can end up producing an unhealthy relationship between citizens and central authorities. In the eyes of the officials, a diverse and autonomous citizenry becomes a monolithic and (ideally) submissive "public." The public must be convinced of the virtues of compliance so that the *herd* can maintain its immunity and remain safe from disease. The more submissive the herd, the greater the opportunity for heroic achievements in disease elimination and the less there is a need for coercive measures applied to dissenting citizens.

Yet the childhood immunization program is the only medical intervention capable of producing injury or death that the state imposes on healthy children. Vaccines are also the only privately manufactured product whose universal consumption is made a prerequisite for participation in public services. These extraordinary exemptions from our normal democratic system of checks and balances and free markets demand extraordinary, and repeated, scrutiny. Vaccine program management must not only work when safety is secured, they must also be robust in the face of safety failures.

But how robust can our system of vaccine safety management ever be? If one assumes that program managers are always diligent, competent and correct in their assessments and that the programs themselves unambiguously and universally safe, then these exemptions from our standards of openness are a small price to pay for results. But when there is a possibility of negligence, incompetence, or even well intentioned error, these protections run the risk of perpetuating and exacerbating truly catastrophic failures.

And when things do go wrong, the inevitably defensive reactions can slide down a slippery slope from the prevention of unnecessary panic to the dissemination of propaganda and the suppression of dissent. The resources available to health officials to mount defenses in the face of failure are extensive. Prestigious journals can relax their standards in support of questionable research; at-risk constituencies can mobilize resources to attack discomforting facts; funding agencies can deny resources for

investigations into possible failures; and conscientious scientists can face disincentives (even sanctions) when they pursue unpopular investigations.

One powerful bulwark against such breakdowns is the right of informed consent. Informed consent requires and empowers each citizen to make choices for themselves and their families based on their independent assessment of risks and benefits. Informed consent thereby provides a counterbalancing force against overreaching activities of the state:

- In the absence of an ability to choose between vaccine formulations, combinations and producers, citizens can at least exercise choice with respect to timing and receipt of specific vaccinations;
- In the absence of meaningful product guarantees or warranties, citizens can request and expect the provision of scientific information regarding vaccine attributable risks and benefits;
- In the absence of clear scientific knowledge regarding the immunological mechanisms, failure modes and adverse exposure consequences, citizens can seek, consider and act on information from multiple sources, reserving the right to critical review of official interpretations.

Today, parents who wish to make a different choice with respect to their children's vaccinations face numerous obstacles. They can claim (or feign) unusual religious beliefs. They can resist their pediatrician's advice and risk sanctions of varying severity, up to and including loss of custody. They can postpone the age at vaccination and forego access to most child-care and educational services. Indeed, with respect to the universal hepatitis B birth dose, they often find that vaccination will precede consent. The provision of informed consent, so essential as a counterweight to state power, remains a distant promise. The updated National Vaccine Plan should incorporate the concept of informed consent in Goal 3 and ensure that it functionally operates in practice as part of the Implementation Plan.

A prerequisite to informed consent is the end of vaccine mandates. Vaccine mandates and informed consent are incompatible. The government should never force compliance but rather take all steps necessary, especially in the area of safety, to earn trust and confidence so that patients and parents willingly vaccinate. The American Nurses Association's has taken a position against mandatory vaccination as a requirement for licensing, stating in public comments on the NVP: "We maintain that such coercive programs are unnecessary, unwarranted, and counterproductive." (p30). We feel this position should be extended to everyone, not just healthcare providers, and the decision to vaccine must be left to the individual/parent in consultation with his/her healthcare provider. Health authorities should accept that not everyone will want to get vaccinated according to the recommended schedule and that some people will prefer alternative avenues to achieve health.

Vaccine mandates also diminish the incentive for enhanced safety. Since federal law protects vaccine makers from liability and favors a mass vaccination infrastructure that enforces compliance through threat of societal sanctions, little incentive exists for

government or industry to address gaps in science and flaws in the system. Only when people are free to reject vaccines they do not consider safe, effective or necessary will manufacturers be motivated to improve on safety and the government truly committed to do a better job of identifying the vulnerable and making vaccine policies more humane and effective.

b. Framing & utilizing cost, benefit, and risk analysis

An honest and comprehensive analysis of vaccine risks and benefits is a requisite for informed decision-making, informed consent, and rational policy choices. Vaccine benefits and risks must be characterized in a manner that is based on extensive science, including emerging science and plausible hypotheses, and on dissemination of the evidence in a way that can be understood by the public, policy-makers, and healthcare providers. Presentation of risk/benefit should be evidence-based, factual and not with the intent to promote coverage. Evidence-based tools should be developed for patients and providers to synthesize vaccine information that facilitates understanding of risks/benefits to enable informed choice.

- The cost/benefit analyses of vaccines and the vaccination program should be done by independent analysts, with economic expertise, not by vaccine developers, manufacturers, or health professionals whose duty is to increase uptake and expand immunization programs. The NVP should specify delegating responsibility for such analyses to an agency not tied to vaccine promotion.
- Estimates and reporting of risks and benefits should use matched framing and be comparable to other approaches used for healthcare interventions, for example, highlighting attributable risk rather than relative risk.
- Analyses should also consider alternative methods to achieve equivalent health outcomes, ie, comparative effectiveness. Two such examples of alternate methods are prevention of Hepatitis B through better detection in hospitals of Hepititis B surface antigen in mothers as compared with universal infant Hepatitis B vaccination, and investment in better hygienic practices in eldercare facilities to reduce spread of influenza and pneumonia as compared with annual flu vaccination of modest effectiveness in the elderly. Analyses should also consider the impact on total health outcomes from a change in practices, for example, the comparing the population effect of lowering asthma rates versus increasing cases of diphtheria, pertussis, or tetanus from delaying the DPT series in infants.
- Calculations of risk/benefit and cost/benefit should incorporate number needed to treat. NTT outcomes should be standardized and objectively defined, for example, focusing not on minor illness or number of disease cases but on serious morbidity or mortality.
- Tools like QALY (quality-adjusted life years) and DALY (disability-adjusted life years) should be considered for both benefits from preventing infectious disease and for risk from vaccine adverse reactions. This would facilitate apples-to-apples comparisons of major/minor adverse reactions with major/minor infectious disease cases.
- Risk/benefit should be calculated for the group of individuals who will receive the vaccine. A number of analyses frame the disease burden based on groups other than

the target group, for example, the mortality from rotavirus or measles within developing countries rather than the target of U.S. children, or the death from influenza among the elderly rather than the target of school-aged children.

- Cost/benefit and risk/benefit analyses should be summarized in format that are easy to understand by the vast majority of the public, and they should be easily accessible and widely promoted so patients/parents can read them prior to going to the doctor's office if they so choose.

Doctors should allow more time to provide the information for informed consent during well baby visits. Physicians should be educated thoroughly on adverse reactions from vaccines, incorporating the newest information, in order to fairly communicate risk to the patient or parent. Doctors should be empowered to make choices and not be de facto forced to promote the recommended schedule under fear of being accused of malpractice.

Many other gaps in safety and cost/benefit communications exist, with related ramifications, and should be incorporated into the NVP.

- Infectious diseases targeted by vaccines vary in their ease and method of transmission and potential for pathology. Herd immunity may have a more or less prominent role in population-level disease reduction for a given vaccine. Different vaccines may have higher or lower efficacy, cost/benefit ratios, and risks. Yet all mandated vaccines are treated as equivalent by health authorities in communications to the public and health providers, especially in regard to compliance with the recommended schedule. More accurate and nuanced communication to the public is needed, and health officials should prioritize their efforts on those vaccines where herd immunity is critical and a high coverage rate is necessary to minimize morbidity. Longer-term, vaccines must be developed that fully protect the individual and do not rely on herd immunity for effectiveness.
- The risk to benefit ratio of a vaccine or vaccine program should apply to the individual and not to the population as a whole. It must be clearly explained to the patient when the benefit for the individual does not exist or is modest and the benefit is primarily or exclusively for the population as a whole or for another group of people, for example, at the final stage of disease eradication or when a flu vaccine for school age children benefits the elderly. We feel that public health authorities should never allow a situation where the individual is required to take the risk when the intervention (vaccination) does not provide sufficient benefit to the individual.
- The vaccine safety procedures in place during manufacturing and distribution and for pre- and post licensing should be clearly delineated to the public. The public should understand how vaccines are made and how they work. This information should address both what is known and what we still do not know and not pretend that gaps in the evidence do not exist.
- Misrepresentations on the VIS should be corrected and the VIS's strengthened to fully support informed consent.
- A goal to disseminate and promote adoption of screening for increased risk for vaccine adverse effects, for example, using newborn heal sticks, genetic tests, or biomarker tests like porphyrins, should be adopted. This information on one's own individual risk would greatly advance informed decision-making.

Cost/benefit and risk/benefit analyses tend to be overly optimist about benefits and to downplay real costs or attendant risks. The NVP should address these deficiencies and support the need for mechanisms to rectify them.

- Costs and risks related to the need for boosters due to loss of immunological memory should be factored in. The original cost/benefit assumptions used for first recommending a vaccine may no longer be valid if they did not consider the need for boosters, which may only be recognized as necessary later. When such new information arises, it should trigger a re-analysis of the cost-benefit calculation.
- The benefits from vaccination should be based on or verified with hard data and not rely only on models which may have incorrect assumptions. Examples for over-reliance on models of questionable rigor include those for HBV infections and for annual deaths from influenza. [5]
- Benefit calculated as reduced risk from the preventable disease should be placed within historical disease rates comparing declines from vaccination with declines when there was no vaccine (eg scarlet fever, malaria in the U.S., tuberculosis in developed nations) in order to assess what proportion of disease reduction can be firmly attributed to the vaccine and what proportion is due to other factors like better nutrition or sanitation or use of antibiotics.
- There are opportunity costs to giving vaccines which should be factored into these analyses. The more time a patient spends with the doctor, the better the patient care. Vaccination administration takes up a large portion of the time of the well baby office visit, taking away from the time spent with the pediatrician.
- There are safety issues related to vaccine manufacturing or delivery practices, such as disease from needle sticks, non-sterile products, and vaccine failures. These health outcomes should be factored into risk/benefit calculations.

c. Legal issues and compensation

Congress set forth in the 1986 law an express policy of identifying and eliminating vaccine injuries and deaths with strong safety provisions and a commitment to take care of injured children with a federal no-fault non-adversarial family-friendly compensation mechanism. Neither of these goals has been achieved, thereby increasing disease burden and lowering public confidence. Minimizing vaccine risks coupled with denial of compensation is a violation of the public trust and a miscarriage of justice. If anything, compensation should be maximized for the individual who assumes the risk for the greater good.

We must have a responsive and meaningful compensation system to uphold public trust and as a point of fairness. The original intent of VICA was to establish a low cost, non-adversarial alternative to suing in civil court, a means for rapid compensation of families suffering from vaccine injury. The Vaccine Injury Compensation Program has veered far from the original intent, approaching the management of compensation as one of resistance to granting awards, with a consequence that only a fraction of the injury set aside has ever been paid out. If it is to exist, VICP needs to be restored to its original intent. The NVP needs to include in its objectives a reform of VICP.

- The vaccine safety infrastructure has to include appropriate data and surveillance that can inform an appropriate compensation system. Scientific information is desperately needed by the VICP lawyers and Special Masters. The IOM has found that data is lacking in over half the situations they reviewed.
- VICP must be fully funded as more claims are filed and injuries added to the table, and VICP resources must be kept separate from the rest of the vaccine safety enterprise funding, including funding for IOM reviews.
- If the vaccine injured must enter the VICA program before going to civil court, then there should be a full look back to October 1988 with no statute of limitations time constraints and a full opt-out to go to civil court after 240 days with no final judgment and only one extension of 60 days for a total of 300 days.
- If a vaccine is found to have a causal relationship to the injuries the injured claims, then the injured should be able to file a claim in VICA with no time constraints. For example, it has only recently become officially accepted that the SV 40 virus from the polio vaccine of the early 1960's may increase risk of brain tumors in older individuals. These people should be allowed to pursue compensation under VICP once the scientific evidence is in.
- The Table of Injuries is the heart of VICA. If an injury meets the preponderance of evidence in a VICA or a civil court claim that the injury was caused by vaccines, then the injury should be added to the VICA Table of Injuries immediately and the VICA administrator should inform all claimants previously denied for the same or similar injury that their claim is now recognized as a compensable event. The injured should have one year to file their claim from the date of notice.
- The advisory panel that evaluates and adds to the Table of Injuries should be constituted of 30% parents/vaccine-injured.
- If the claimant gets a VICA award, then they should be entitled to any post judgment interest. Many times after judgment, a case is appealed time after time, and some families wait years to receive compensation. We believe if the government had to pay interest on a claim after a positive judgment, it would ensure timely payments.
- We recommend that the VICA program approve any claim based upon the medical records in lieu of a hearing. If the claimant's medical evidence substantiates an injury that meets the requirements on the Table of Injuries, claimant must be approved without hearing, further discovery or delay. Said review should occur within 120 days of receipt of all necessary medical records in accordance with HIPAA. This would help to make VICA the true no-fault, non-adversarial program it was intended to be.
- VICA is prohibited from paying for studies with money allotted to VICA to fund vaccine injury judgments. VICA money has been used to pay for one-sided studies to be able to turn away claims; this practice must end. Rather, research money should come from Congress allocated to an independent vaccine safety agency, and these funds should help to determine causation for table injuries. Studies to be conducted should be determined every six months through a formal review process by the Congressional Committee with oversight over VICA in conjunction with the vaccine safety agency. Studies must be conducted by individuals free of conflicts of interest. Formal reporting of results, including any impact on the Injury Table, must be made expeditiously to the Special Masters.

- The death claim should be raised to $1,000,000. Medical, physical/occupational therapy, rehabilitation, medical monitoring, special diets, supplements, and educational/tutorial therapy expenses incurred from injury should be paid without limitation.
- The pain and suffering cap of $250,000 should be deleted; there should be no cap on pain and suffering. The monetary award should be determined on a case by case basis. Some cases deserve more than others.
- Parents with an injured child should be able to file a separate loss of consortium claim though the VICA program. Said filing by injured claimant should toll federal and state statutes of limitation and repose for any available loss of consortium.
- The vaccine injured should be able to file a punitive damage claim with no caps. The monetary award should be determined on a case by case basis, as all cases differ. If it is proven, as it was with tobacco, that companies hid information about a vaccine's or an ingredient's detrimental effects, parents should be able to file a case for punitive damages.
- Compensatory damages should include but not be limited to: past, present and future medical treatments, drugs or devices for said injury, physical/occupational therapy, rehabilitation, medical monitoring, special diets, supplements, educational/tutorial therapy and any other treatments/medical/therapy needs as deemed by the treating physician. We have spoken with many parents who have won in VICA only to have Justice Department attorneys with endless time, money and energy deny claim after claim, even when claims are made by reputable physicians.
- If the claimant develops a new condition as a consequence of his/her injury that requires an added medical treatment, drug or device then said claimant should be able to petition to modify the judgment for additional compensation, award or payment due to said medical condition or availability of new therapy. The causation of said medical on additional injury should be by the treating physician's statement.
- Regarding allotment of funds once a claim is won in VICA, experimental and medical necessity defenses as reasons for denial should be abolished in making a decision on how a judgment can be spent. Deference should be made to the treating physician. If the treating physician says that a medical treatment, therapy, drug, supplement, diet, etc. is needed for the vaccine injured's health or well-being and as a consequence of the vaccine injury, then it should be approved. Parents should not have to have the burden of proof to obtain coverage for their child's needs.
- Rent, clothing and food should not be counted in any asset determination or as a qualification of determining availability of any Federal, State or Benefit program. VICA should provide the amount of any judgment.

VICA should be an optional program, thereby incentivizing industry and the program to work together to maximize the usefulness of the Table as a basis for carrying out the Congressional mandate of a non-adversarial, swift and generous alternative to traditional state tort law remedies to protect both the vaccine program and those injured in the war against disease. There should be no constraints on post-program civil litigation, e.g. FDA preemption, limits on warning and design defect claims, ban on punitive damages, caps, etc. Patients should enjoy the full protection of their state law as such remedies are a vital part of our common law tradition that, together with appropriate regulation, ensures the safest possible products.

d. Reducing unnecessary industry protection to enhance safety

One of the original intents of VICA was to protect vaccine manufacturers from liability, so they would remain in the vaccine business. This was an era when profit margins from vaccines were low, government pressure kept prices at commodity levels, and government assistance was needed to expand coverage to low resource nations. Today, the private manufacturing sector is in robust health, vaccine profits are high and growing, and vaccines created for developed countries are of modest use in the second and third worlds, which have now developed their own production capacity. It is arguable that continued protections are needed to satisfy concerns that litigation will destroy the domestic or global vaccine industry.

In the U.S., preemption of traditional tort remedies through VICA and protection of industry from product liability claims have reduced the normal marketplace incentives on manufacturers to ensure the safety of their products. As noted above, VICA should be viewed as an alternative rather than a replacement remedy. VICA should not compromise any substantive right, regulations, procedural or evidentiary right that is afforded to claimant under color of any state's law. VICA's statute of limitations should not preclude legal remedies at the state level under their existing laws for minors. The view recently articulated by the Georgia Supreme Court in Ferrari is a superior position to insure vaccine safety. In other areas such as drugs (Levine v. Wyeth) the Supreme Court has viewed the traditional tort system as administered by state courts necessary to insure consumer safety. Federal regulatory oversight alone is inadequate to ensure the safety of medical products.

A related consequence of the vaccine injury policies exempting manufacturers from product liability has been the absence of free market competitive pressures for quality results. As the quality revolution in management swept through the business world in the latter part of the 20th century, most competitive industries have embraced quality disciplines that have not yet penetrated the immunization enterprise. The pursuit of zero defects in vaccines would encompass not just efficacy but also a performance standard of zero adverse events. Such a goal need not be immediately attainable, but the relentless focus on continuous improvement toward that goal would mean that no disabling injuries or deaths would be viewed as acceptable. Instead, every adverse event would be managed as an opportunity for analysis of the root causes of vaccine failures. Instead of encouraging reclassification of adverse events as coincidental or unavoidable events, severe reactions would be treated with respect, compassion and curiosity. But as Philip Crosby describes it, Zero Defects (in this case Zero Adverse Events) is a cultural attitude, one that would require sweeping changes in all aspects of vaccine safety management. Culture change can only come from the top. As the guiding document on the vaccine enterprise from its leadership, the NVP should be at the forefront of changing such cultural attitudes. This brings us to the conditions and context for leadership on vaccine programs and safety, in other words, vaccine governance.

Re-Engineering Vaccine Safety Governance

a. Monitoring, evaluation and enforcement of vaccine safety

The National Vaccine Program, established in 1986, was supposed to provide "coordinated direction" of the U.S. vaccine enterprise. While it might be argued that the program has led to many new vaccines being developed, licensed, and mandated, similar progress in safety has not been realized. While DTaP and IPV may have a better safety profile than DTP and OPV respectively, it is hard to argue that the newer MMRV or Gardasil have superior safety profiles to the Hib or Hep B products, licensed two decades earlier, or that the track record of approval of safe vaccines is any better recently, for example, with RotaShield, than it was, for example, with the 1960s Inactivated Measles Vaccine. Not surprisingly, vaccine safety gaps have been described in numerous government and IOM documents spanning the last two decades, and the gaps persist today. For example, a 1994 IOM report noted these deficiencies:[6]

> The committee was able to identify little information pertaining to the risk of serious adverse events following administration of multiple vaccines simultaneously. This is an issue of increasing concern as more vaccines and vaccine combinations are developed for routine use. Both pre- and postmarketing research should address the issue**…**
>
> The committee was able to identify little information pertaining to why some individuals react adversely to vaccines when most do not. When it is clear that a vaccine can cause a specific adverse event, research should be encouraged to elucidate the factors that put certain people at risk for that adverse reaction**…**

The lack of progress suggests that more than another report is needed, but rather real structural change. Performance management of vaccine safety is mostly nonexistent. If a rigorous safety science program is developed, it is unclear who will develop it and oversee its implementation, to whom it will report, how often, or in what way, or how success will be determined. There are no accountability or evaluation criteria for progress against goals, effectiveness, timeliness, ROI, or comprehensiveness. It is unclear to whom the various agencies involved in vaccine safety should report, how, or when. The situation that led to the thimerosal example with the FDA being "asleep at the switch" and no one responsible for calculating total mercury exposure still exists. Oversight and accountability remain fragmented and incomplete, with responsibilities spread among IAVG, NVPO/NVAC, VICP/ACCV, IPAC, MIDRAC, NIAID, CDC/ACIP, FDA/VRBPAC, DoD, AFEB, USAID, the Veteran Affairs Administration and state and local governments. [7] Although NVPO was charged with making sure NVP was/is implemented and that terms in the 1986 PHS law are met, it has no enforcement ability, redress mechanisms, or budget to make sure the goals are accomplished.

To correct structural governance deficiencies, we support the creation of a vaccine safety agency (VSA), similar in concept to the National Transportation Safety Board. Established by Congress, the VSA would be the lead Federal organization on vaccine safety. It would operate independently of other agencies including HHS and answer directly to Congress and the President. It would have its own staff, strategic plan, and a

budget of at least $100 million annually, appropriated by Congress. A small percentage of the subsidies now given to vaccine manufacturers could easily be allocated to the VSA, making its operation revenue neutral. The VSA oversight board, appointed by the president, should be larger than NTSB's 5 members, with the majority being consumers/parents who have the most at stake from enhanced vaccine safety. The board would obtain expert advice from a range of scientists and healthcare professionals.

Unlike NTSB, the VSA should have the authority to enforce changes based on its report findings, in order to prevent future adverse effects of vaccines, and would have responsibility to monitor whether its recommendations have been adopted. Its recommendations would be given priority attention at other agencies like FDA, CDC and NIH. The VSA should have the power to prevent the universal mandate, widespread use, or licensure of any vaccine that it feels has not been adequately tested or has been found to have a substandard safety profile. Its report to Congress should be annual, cover the status of vaccine safety activities across all federal agencies including pre- and post-licensure activity and developments in basic science and infrastructure, and assess the status of adoption by other agencies of its recommendations to modify practices.

Besides an effective governing structure, the current vaccine safety system lacks consumer stakeholder involvement and transparency. Parents and adult patients are the real customers of the immunization program and the only parties without a conflict of interest and with a true interest in outcomes. Public health officials must be more accountable to parents than to industry. Yet all existing advisory committees which have immunization responsibilities - ACIP, ACCV, NVAC, VRBPAC – have token parent/consumer representation and lack diversity of views on vaccine risks and benefits. Patient/parent representatives on these committees should include both vaccine-preventable groups and injured groups, as well as neutral parties. These groups should be integrated into the entire oversight, input, policy, and research implementation process, not just at the beginning or end for public comment or token representation. The opportunity for public input to these committees should be expanded, and the committee meetings should be broadcast in real time via the web.

b. Conflicts of interest in vaccine science and policy

Public institutions have the responsibility to carry out public affairs with governance mechanisms that keep decisions free of conflicts of interest and resultant self-dealing by interested parties. As our society has involved, the influence of well-organized and well-funded interest groups has made avoiding such conflicts of interest progressively more difficult. In the area of vaccine safety, we see serious conflicts between the promotion and management of the childhood immunization program and the exercise of diligence and care in the safety monitoring of the program. These conflicts play out in numerous ways. Indeed, despite many years of effort by dedicated consumer advocates, we fear that vaccine program governance has deteriorated to a point where the most economically interested parties have effectively collaborated to dominate decision-making in ways that maximize their direct benefits, while marginalizing the concerns and complaints of dissatisfied customers of the vaccine program. These parties—vaccine manufacturers, scientists and academic labs supported by industry through direct funding or through patents, health maintenance organizations (HMOs), pediatrician groups and government

public health officials—have demonstrable interests in favor of expanding vaccine administration; they also have an interest in constraining vaccine safety initiatives and in some cases suppressing unwelcome findings. We'll focus on three of these groups.

Health maintenance organizations. HMOs face the unique challenge of maintaining profitability in the face of skyrocketing health care costs and pressure from their own customers, primarily private companies seeking to minimize the cost of providing health care benefits. In pursuit of their profit goals, these insurers have clear interests in minimizing the cost of their service obligations and reducing the variability of their patient risk profiles, while also projecting an image of responsive service and high quality care to their patients. Because of the known turnover in their patient bases, HMO *investments* in health and prevention require relatively short payback periods; by extension, long-term risk reduction and chronic disease prevention are unlikely to receive HMO financial support. By contrast, childhood vaccinations provide a strong economic benefit to HMOs: they provide visible services to young families; the unit of service delivery (the well child visit) is highly predictable, highly scalable and therefore low cost at the delivery level; and they prevent less structured (and potentially higher cost) care delivery in the case of children infected with a childhood disease. The main economic goal of HMOs lies in limiting the number of well child visits, one reason why combination vaccines have proven popular. The potential adverse consequences of an expanded childhood vaccine program (and expanded vaccine combinations) are either out of their services scope (e.g., autism and other developmental disabilities) or beyond their preventive planning horizon (e.g., asthma, diabetes, cancer).

Pediatricians. One consequence of the cost squeeze in health insurance has been that pediatricians, like most primary care physicians, have become captives of a new economic model of primary care delivery: high volume, low touch, and increasingly structured around compensation rules for specific diagnosis codes rather than time spent with children. Most pediatricians enter the field of pediatric medicine out of a desire to serve children. Increasingly, they are becoming captives of the compensation rules regarding allowable services. One of these allowable routines is the well child visit, a repeatable and tightly defined procedure that has evolved into little more than a tollgate for vaccine administration. The economics of pediatric practice have become increasingly dependent on these tolls, and the well child toll has become a critical component of a pediatrician's annual income.

By contrast, as the front line of vaccine adverse effect reporting, pediatricians have incentives to avoid adverse event reporting. When faced with a possible vaccine adverse event, each pediatrician has discretion in associating the event with the vaccine. Pediatricians have a personal stake in the success of the vaccine program and, more important, an emotional stake in the absence of causal relationship between vaccination and injured children. No pediatrician wants to believe that their personal interventions have caused harm to their patients. At the same time, the report of an adverse event takes time and effort while also encouraging litigious behavior on the part of parents, none of which would benefit the pediatrician. Not surprisingly, the groups that represent pediatricians seek to minimize the concerns over adverse events and preserve the confidence of parents in the childhood immunization program and its associated well child visit.

Public health officials. Public health officials in positions of vaccine policy leadership typically have sustained long careers in the field and have participated in the long trail of policy choices that have produced the current expansive strategy. These career officials draw meaning from this legacy of work and often reveal their search for meaning by seeking other ways to expand their mission, either through heroic efforts at disease eradication ("Worldwide elimination of hepatitis B transmission: we have the way we need the will") or global collaborations to spread vaccine successes to new countries. They certainly have little appetite for seeking evidence that might constrain this mission or, what would be far worse, to demonstrate that it might have inflicted more harm than good.

As the regulatory hub for the field of vaccine development, these officials interact regularly with interested parties in the vaccine program: the vaccine manufacturers, the HMO industry representatives and pediatrician groups. After many years of collaboration in this community (what Eisenhower might have called the *vaccine development complex*), they may become friends, certainly develop mutual respect as colleagues and support a range of professional and social contacts across the community. Many "retire" to work for industry or organizations supported by industry. Those who may question or criticize their mission are threatening and unwelcome. Frequently, those who raise questions are shunned (if insiders) or labeled as "anti-vaccine" or "junk scientists" (if outsiders). Effective dismissal, however, requires the larger scale denial of resources for which these officials serve as gate-keeper: they deny funding for legitimate vaccine injury hypotheses; they deny independent access to vaccine safety data resources; they forego deep investigations into adverse consequences; and they effectively deny meaningful access and participation to the interested and injured parties.

The longstanding commitment of these groups which form our public health leadership to expansion of the mandatory vaccine interventions places pressure on the watchdogs of safety to make safety administration friendly for new vaccines and represents a central fallacy of modern vaccine policy: if some vaccine interventions can do good, then more interventions will be better. The sentiment among public health officials that failure to expand the vaccine program would be a "tragedy" reflects this premise, shared by so many, that we have only just begun to harness the potential for a new strategy of intervention. Numerous careers, major research programs and large-scale commercial investments have been bet on the promise of these interventions. Much is at stake and the stage is set for rampant conflicts of interest on immunization to permeate science, medicine, and public health.

These individuals and groups focused on vaccine promotion seem incapable of separating vaccines' benefits from their risks, as if the high benefits absolve responsibility from decreasing adverse events. A simple analogy is justifying and allowing 5,000 serious injuries if 5,000,000 escape infectious disease, when in fact if safety were addressed, the 5,000 injuries could be reduced to 500. NTSB officials do not talk about the value of aviation to society when they investigate a crash; they figure out why it happened and put new processes in place to prevent future mishaps. Those involved in vaccine expansion rarely approach safety in this manner. Underlying conflicts of interest interfere with such thinking and are a primary reason for needing a truly independent vaccine safety agency.

Besides general thinking patterns reflective of bias, direct COI can be seen in many vaccine safety activities. The researchers who test vaccines for licensure for the vaccine manufacturers are frequently the same ones the CDC uses to assess post-marketing safety, certainly a conflict of interest. This includes VSD investigators at HMOs, the investigators of the Finnish MMR study and the Italian DTP study on thimerosal, as well as Drs. Pichichero and Treanor who wrote several papers absolving thimerosal of safety issues, yet whose institution is largely funded by vaccine royalties. When high profile safety investigations have taken place, these investigations were carried out by interested parties. In the case of three recent thimerosal studies in Denmark, for example, the primary authors for all of them were directly employed by a vaccine manufacturer or its affiliates with direct profit interests in the products involved.

The CDC has tried to separate vaccine risk management from risk assessment by setting up the ISO, but as long as the ISO is part of CDC or HHS, the separation is insufficient. The CDC's primary focus is on vaccine promotion, and HHS has inherent conflicts due to being a VICP defendant. Just as Congress moved the NTSB out of the FAA and the DOT, a vaccine safety agency should not be part of CDC or HHS. The NVP should make explicit recommendations to end any practices that involve conflicts of interest.

c. Policy response to safety signals or inadequate evidence

We recommend that vaccine policy makers adopt the precautionary principle when making decisions on vaccine recommendations when concern has been raised about a potentially adverse outcome. The precautionary principle, well developed in the environmental field, is defined as follows: [8]

> The **precautionary principle** is a moral and political principle which states that if an action or policy might cause severe or irreversible harm to the public or to the environment, in the absence of a scientific consensus that harm would not ensue, the burden of proof falls on those who would advocate taking the action. The principle implies that there is a responsibility to intervene and protect the public from exposure to harm where scientific investigation discovers a plausible risk in the course of having screened for other suspected causes. The protections that mitigate suspected risks can be relaxed only if further scientific findings emerge that more robustly support an alternative explanation.

Past policy decisions by vaccine officials suggest that the precautionary principle is absent from vaccine practice.

- When MMRV was found to produce more adverse events than the separate MMR and varicella vaccines, the FDA did not pull it and ACIP did not give preference for separate injections. Instead, ACIP just removed preference for the combination vaccine.
- Research on increased risk for schizophrenia from maternal cytokine response to in utero exposure to influenza suggests that flu vaccine itself, given to pregnant women, may generate the same immune response and increase schizophrenia risk. Yet flu

vaccine is routinely recommended for pregnant women, despite evidence that it might not be effective in preventing morbidity from flu.[9,10]

- A DoD vaccine safety team has raised concerns over multiple vaccination, suggesting that as the number increases, so does the potential for more AEFIs. Yet the CDC and FDA have not taken any immediate steps to substantiate or refute the concerns while they continue to approve and recommend more vaccines to be given on the same day.
- Multidose vials were known to be less safe than single dose presentations yet the push to convert to single dose vials occurred only after the thimerosal issue arose and manufacturers were forced to change.
- Mercury and aluminum are known developmental neurotoxins but they continue to be allowed and used in vaccines for infants and pregnant women.

Adoption of the precautionary principle would lead to a delay of the practices noted above, and similar ones in the future, until the safety studies have been conducted. We feel that such a guiding principle would greatly advance patient safety. It would have the effect of tempering the promotion-at-all-costs thinking that pervades the vaccine enterprise.

Prevailing vaccine policy encourages maximum vaccination events, regardless of safety issues, benefits, costs, or comparative effectiveness. We support a more conservative approach to vaccination that gives more weight to such analyses before automatically assuming that more vaccination is the optimal approach.

- Common sense suggests caution in further immunizing someone who has had a previous AEFI, yet this is not part of vaccine practice recommendations. Contraindications should increase, not decrease. Physicians should be given more leeway to make judgments on waiting to immunize without concern about violating clinical guidelines. Clinical judgment that considers patient values along with the best evidence should prevail, especially when adequate research has not been done.
- Comparative effectiveness of titer testing compared to revaccination when a child's vaccination records are missing should be conducted. The assumption is to vaccinate when status is in doubt, even though overimmunization does not provide additional benefit but increases risk.
- The timing of immunization has been crafted around maximizing opportunities to vaccinate, rather than being based on what might be optimal for the child. For example, infant vaccines are compressed into well baby visits, catch ups are encouraged during emergency room or clinic visits when the child is sick, and the first Hepititis B vaccine is pushed during the birth hospital stay. Schedules should be designed around safety considerations, especially around developmental windows (first 6 months of life, puberty) when the immune system is rapidly changing, as well as around extenuating events like concurrent illness, concurrent use of medications, and concurrent exposure to pollutants.
- Many studies have shown that influenza vaccines do not work, especially in the very young and the elderly. The relentless promotion to these groups should be suspended until the science is more developed.
- The official position that every case of a vaccine-preventable disease must be prevented, should be reexamined, including being subjected to rigorous cost-benefit

analysis. For example, if preventing every case of measles requires boosters with attendant risk, diverts healthcare personnel to intensive surveillance from other patient needs, and costs hundreds of millions of dollars more than the cost of simply containing the disease at low levels, is it worth the additional effort and risk, or would those extra dollars be better spent on other health programs like treatments for chronic illness in children?

- As new types of vaccines are produced, like recombinant DNA vaccines, we need to thoroughly understand their effects over the long term before allowing widespread use, especially in children. The public should be informed about what is being done to increase the safety of vaccines and what the next generation of vaccine design will bring in terms of safety profiles. Concerns are already increasing over the ingredients in the swine flu vaccine being developed, including new and multiple adjuvants.

We are concerned that vaccines are licensed or recommended without adequate testing or monitoring in the vaccine's target group. The FDA could and should require manufacturers to conduct primate studies of the full vaccine regimen, and it should require any new vaccine to have extensive animal testing as part of a vaccinated versus unvaccinated regimen. A vaccine's adverse event profile should be known before mandating so that the injuries can be added to the VICP table. FDA has recently asked VRBPAC to vote on "blanket safety and efficacy" without considering caveats to the license, for example, the vaccine has not been tested in younger children; ACIP then has no limitations on its recommendations for use. Before a provisional licensing approval by FDA or ACIP mandate, randomization in the target population and tracking for several years should be required. Even though this will delay universal use, it overcomes problems of not being able to detect adverse effects once uptake is universal. ACIP should not approve a vaccine for universal use until the vaccine has been in limited use for long enough for adverse reactions to be detected. Even more disturbing, manufacturers are trying to minimize their financial risks from development costs by asking for a pre-commitment from ACIP that if a vaccine is licensed, it will be approved for universal use. This practice would subvert safety goals unless a time lag is built in to the approval process to allow for signal detection of adverse events as the vaccine is put into use.

We feel that official policy favors industry interests over those of consumers and recommend that the NVP include language that elevates the importance of patient health and patient safety over concerns for market stability and growth.

We recognize that maintaining a successful vaccine program requires the participation of a viable base of vaccine suppliers. These suppliers deserve the opportunity to make competitive, market returns on their investment, consistent with their risks and investments. Increasingly, however, the "market" for vaccine suppliers has become a regulated state oligopoly, not really a market at all, but rather a highly managed public-private partnership with guaranteed returns and minimal risks. Large, stable and growing markets are guaranteed by official decree. Product liability is more constrained than for any other manufactured product. New firm entry is highly constrained and only a small set of competitors share the market, with a small number of competitive formulations granted market access at any point in time. Public health officials, in their quest to serve

their suppliers, have overshot the goal and have effectively become supplier advocates, consistently acquiescing in decisions that benefit vaccine manufacturers and disadvantage consumers.

The extraordinary profitability of pharmaceutical manufacturing (the 2001 profits of the top 10 pharmaceutical manufacturers exceeded the profits of the rest of the Fortune 500 combined) can make vaccines appear unattractive as a business and drug manufacturers have long complained about the poor relative profitability of their vaccine divisions. This performance profile has shifted as new, patent protected products with high prices and healthy margins have replaced older vaccine formulations in the product mix. And while decisions to endorse and promote the strategic expansion of childhood vaccines with increasingly small incremental consumer benefits has provided large financial benefits to these companies, the management of safety concerns has consistently placed manufacturers' interests ahead of those of consumers. Despite demonstrable health threats, recalls of dangerous vaccine products are a rare event. Remarkably, polio vaccines contaminated with highly carcinogenic viruses were never recalled and have now been associated with widespread cancer incidence. Similarly, longstanding calls to recall vaccines containing the highly neurotoxic element, mercury, have gone unheeded, with unknown developmental consequences in the millions of children exposed after the risks of mercury exposure were first identified. Even now, new flu vaccine formulations containing mercury have received CDC endorsement and it is likely that the new swine flu vaccines will contain thimerosal. Meanwhile, sensitive safety investigations into vaccine failures have been entrusted, in some cases, to vaccine manufacturers themselves and, in others, to researchers with close financial ties to manufacturing companies. Not surprisingly, the research results of such investigations routinely find no adverse consequences of vaccine exposure.

In the last 20 years, while we have had the highest percentage of children vaccinated in history, at an earlier age and with more vaccines, we have also seen the highest number of chronic health conditions in children ever reported. Is this a coincidence? We will never know unless the Federal government makes a commitment to find out. The NVP is the right place to see if this commitment exists.

d. Ethics and values

Official vaccine policy and practice embody a value system that places the public good above that of the individual and that assumes the superiority of vaccination over other health strategies or healthcare needs. We would like the NVP to affirm the higher value of the individual in healthcare decisions, recognize the possibility that approaches to health other than vaccination may be valid, and require objective prioritization of vaccine spending within total healthcare spending demands, prior to further expansion of vaccine programs.

We have observed devaluation of the individual in several instances and the ethical questions it raises. We question the ethics of shifting of vaccine risk from one group to another, for example, recommending influenza vaccination in young children, labeled as vectors, in order to protect the elderly who do not mount adequate immune response, so that the children assume the risk. We question whether individuals who have a high risk

profile for vaccine adverse effects should be pressured to vaccinate for diseases with a low transmission rate or low risk of serious morbidity to that individual.

Vaccine expansion promoters complain that the vaccine enterprise is under-funded but these assertions lack substantiation. Coverage rates are very high and much higher than in the late 1980s. Remaining potentially vaccine-preventable diseases are not the most pressing health concerns of Americans. We are concerned about budget priorities that allocate billions of dollars to development of new vaccines for diseases with modest significance to our population or for hypothetical disease threats, while funding needs for more debilitating chronic diseases like autism and learning disabilities are unmet. We are concerned that vaccine expansion programs are funded to the detriment of vaccine safety program support. That Federal agencies would even look to the VICP funds for vaccine safety research dollars or IOM reviews is unconscionable when billions are being given to private interests for vaccine expansion. We feel that the Federal government is overinvesting in vaccine promotion when money could be better spent on other pressing healthcare needs. We would like to see an external, unbiased party to calculate return on investment for vaccine expansion activities relative to other healthcare activities.

Most of the horrific infectious diseases of the past have been conquered without vaccines, including scarlet fever, syphilis, and tuberculosis. Many routes to health from infectious disease exist, and more consideration should be given to alternate practices. For example, the latest swine flu scare may be due to livestock raising practices. Reform of these practices might be a better investment than creating and administering another vaccine.

We are concerned about the long-term, overall effect of the current expansionist vaccine strategy and would like to see this concern addressed in the NVP. Through the 1970s, the childhood immunization program consisted of interventions against a short list of diseases: smallpox, polio, diphtheria, pertussis and tetanus. Today, the list has multiplied to include vaccines against measles, mumps, rubella, hepatitis B, hepatitis A, haemophilus influenza B, varicella, pneumococcal and influenza. Before they reach their second birthday, a child born today will receive over 30 different vaccine antigens when following the recommended program. With these additions, we have embarked on a public health strategy that represents a radical shift in the way our species experiences its environment. In a quite literal sense, we are in unexplored territory. Just as large-scale industrialization has had frightening effects on our environment, a large-scale vaccination regimen may plausibly lead to adverse effects on human health of similar magnitude. Until we understand the long-term effects of vaccine proliferation, we should not continue to uphold a value system that views any newly licensed vaccine as an automatic blessing to mankind.

The current value system that views the present rates of acute and chronic vaccine-caused disease as “acceptable losses” due to vaccines’ high reported benefits is intolerable. Besides enhancing the science of adverse outcome mechanisms and susceptible populations, adverse reactions can be minimized or eliminated through a variety of measures. These include vaccine redesign, reliance on antivirals or other public health measures to reduce the burden of infectious disease, alternative schedules, avoiding multiple vaccines on a single day, more restrictive contraindications, and screening for individual susceptibilities. Any argument to the contrary denies the power of science and

places administrative convenience and vested interests over the ethical and legal obligations to each individual patient.

As we have stated above, the overarching goal of the NVP should be better health outcomes for America's children. Vaccine programs to combat infectious diseases can be a valuable part of strategies to advance the mission of childhood health. These diseases, however, reflect only a fraction of the adverse health outcomes facing children today and a *decreasing* fraction of these. The earliest vaccines—polio, diphtheria, smallpox—protected against highly infectious and frequently fatal diseases, diseases to which infants were also highly vulnerable. More recent additions to the vaccine program do not share the same attributes or obvious benefits. They are often less dangerous to children (chicken pox or rubella, or rotavirus in U.S. infants), less infectious (haemophilus influenza B or pneumococcal) or otherwise less prevalent among children (hepatitis B).

Public health officials collect and propagate asymmetric information with respect to the total health of children and how it is changing. Infectious diseases, even hypothetical threats like SARS and avian flu or ones with even the smallest number of cases like recent measles outbreaks, are touted with the greatest of alarms, while skyrocketing rates of other disorders like autism are minimally addressed and dismissed as part of the human condition. At some point the disregard of true disease threats must reflect a conscious choice to forego the acquisition of unwelcome knowledge, an attempt to preserve plausible deniability in the face of disturbing news. In the year 2000, there were 122 cases of AIDS reported in children under five years of age, 37 cases of measles, 57 cases of mumps, 10 cases of rubella, 43 cases of hepatitis B, less than 3000 cases of pertussis, and zero cases of tetanus, diphtheria and 9 other notifiable diseases. By contrast, California, with over 10% of the U.S. population, reported over 6,700 new cases of PDD/autistic disorder, by extrapolation a national reporting rate of 70,000 children annually. Over 800,000 children under five reported an episode of asthma. New juvenile-onset diabetes cases probably numbered in the thousands, but no reliable surveillance exists. We do not presume to judge the *relative* significance of these diseases to childhood health, however we do submit that chronic diseases are in no way *less* harmful to children. We would also note that the vast majority of children *recover* from a case of childhood infectious disease (as parents looking back on our childhood, most of us remember uneventful recoveries from these diseases as children). To rectify this asymmetry, the NVP should be positioned within a broader plan for total health for children, and the concept of "the greater good" defined to mean what activities will generate the most benefit for children. For American children, we would guess that more "good" will be generated by tackling chronic diseases, not developing another vaccine.

Finally, the prevailing value system of the vaccine enterprise holds a condescending, trivializing and unwarranted view of the role of parents in upholding their children's health and making choices for their family's health. This may be one of the underlying reasons for the recent deterioration in public trust in vaccination. Diligent, concerned parents have become the most vocal critics of our public health officials' performance in the area of childhood health. It is true that, while parents may know a great deal about an individual child, they inevitably possess a limited view of populations, enhanced perhaps, but quite possibly distorted, by shared group experiences in advocacy groups. Scientists typically rely on more rigorous surveillance to provide reliable trend and incidence data.

Yet scientists, doctors and other "experts" will only know what surveillance and science tells them, and when basic surveillance and science are lacking, they become less reliable sources than parents, absent a primary information source. Until reform of the vaccine enterprise is realized and a vigorous Vaccine Safety First agenda exists, parents collectively will be the most accurate repositories of information for what helps or undermines their child's health. Going forward, a Vaccine Safety First agenda will go a long way to support parents and individual patients as they make decisions for their health in consultation with their healthcare providers. The NVP, by encompassing principles of Vaccine Safety First, can help restore trust in vaccination by showing that the Federal government values the role of parents and patients within the vaccine enterprise; ultimately, it can be a vitally important mechanism for advancing optimal healthcare choices by Americans.

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