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Influenza vaccine failure: Failure to protect or failure to understand?

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Abstract

Introduction: I propose that influenza vaccine failure be defined as receipt of a properly stored and administered vaccine with the subsequent development of documented influenza. Several mechanisms of vaccine failure occur and can—sometimes in combination—lead to what is termed "vaccine failure." Influenza vaccine failure occurs for a variety of reasons, many of which are not true failures of the vaccine (e.g., improper vaccine storage and handling).

Areas covered: In this article, I discuss common causes of "vaccine failure" that are appropriately or inappropriately attributed to vaccines. This includes host, pathogen, vaccine, and study design issues such as, genetic restriction of immune response; failure to store, handle and administer vaccine properly; issues of immunosuppression and immunosenescence; apparent but false vaccine failure; time-mediated failure; and others.

Expert commentary: A proper framework and nosology for vaccine failure informs discussion about influenza vaccine efficacy and prevents misperceptions that in turn affect vaccine uptake. Influenza vaccine can only provide maximum protection to the extent that the circulating and vaccine strains closely match; the vaccine is stored, handled and administered properly and within a time frame to result in development of protective levels of immunity; and is administered to a host capable of immunologically responding with protective immune responses.

Keywords

Vaccine Storage; Immunity; Immunization Programs; Influenza; Human; Influenza Vaccines; Vaccination

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Declaration of interest

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1. Introduction

> “Language is conceived in sin and science is its redemption.”
>
> - Willard van Orman Quine

Definition and consensus is needed in regard to the term “vaccine failure”. Lacking such definition, professional and lay media use the phrase “vaccine failure” often without defining the meaning and purported mechanism behind the use of this phrase. Such is the case at the time of this writing (January 2018), where estimates that this year’s influenza vaccine is “only about 30% effective” in the US and about 10% effective during the past winter season in Australia are proclaimed, suggesting that the vaccine is “ineffective” and has “failed”. Similar alarming reports have been published over recent years. In this paper I will propose a structure and nosology for discussion regarding the term “vaccine failure” and will use influenza vaccine as an example.

The Centers for Disease Control and Prevention (CDC) recently summarized influenza vaccine effectiveness studies since 2004 on their website[1] and they are illustrative of the issues discussed in this review. In this summary, CDC notes that their estimates are based on observational studies conducted since 2003, and uses medically attended outpatient visits (some years inpatient hospitalizations were also counted) with laboratory confirmed (rRT-PCR) influenza as the outcome measure, through the US Flu VE Network (consisting of five study sites across the US). These estimates (see Table 1) are further adjusted for variables such as age, sex, and medical condition of the subject, study site, and others). This study design is important in that such effectiveness estimates have important limitations including an observational study design, estimates based on potentially small numbers (depending upon age in sub-populations), study outcomes generally limited to outpatient illness, variations by population and geographic location studied, the outcome measured, and other variables as explored in this review. The net result is generally very wide confidence intervals around the point estimate (see Table 1).

As a case study for use in this review, I have chosen a 2018 MMWR report from US Flu Effectiveness Network, funded by the CDC, which reported an overall 36% (27 to 44%) effectiveness of the 2017–2018 seasonal influenza vaccine. For influenza A/H3N2, no effectiveness was reported for any age group except 6–18 month olds (51% with 95% CI of 29–66%)[2]. These reports of low effectiveness were widely reported by the media, trumpeting that the vaccine was ineffective. These estimates were the measured effectiveness across a small population (4,562) of subjects across the age spectrum (leading to small numbers in each age strata). This report is chosen for comment in this article, as the methodology for that study is available and serves as a good example of the discussion and debate regarding the commonly voiced concern that “flu vaccines don’t work.”

In this study, closer scrutiny reveals that this was an observational study design (i.e., confounding and bias issues may exist): the study included a small sample size with consequent wide confidence intervals; subjects were considered vaccinated if they received ≥1 dose of vaccine at least 14 days earlier (recognizing that young children need two doses for full immunization in the first year they receive vaccine); results were not adjusted for

chronic medical conditions, severity of illness, or functional status, only medically attended acute respiratory illness (MAARI) was used as the outcome; immunization histories of younger children were often unavailable, and self-report of immunization status was accepted.

While the focus of this paper is *not* this particular study, it is illustrative of the problems associated with such studies that report influenza vaccine effectiveness (prevention of illness in vaccinated populations), efficacy (prevention of illness among vaccinated persons enrolled in controlled clinical trials), or vaccine failure (documented influenza despite documented receipt of influenza vaccine). This mirrors part of the common complaint among patients that they received influenza vaccine and yet "got the flu—the vaccine failed." Such nosology has a powerfully negative effect, increasing mistrust in both the public and providers' minds about the value of influenza vaccine—with consequent low coverage rates. How we define the term "vaccine failure" has tremendous implications for how we think about, study, and measure vaccine failure; how we interpret the results of those studies; how we report it to the public, health professionals, and the media; how we formulate public policy as a result of such study findings, how it may or may not motivate research toward a more effective vaccine, and how it eventually impacts vaccine uptake and health care costs.

2. Is This Actually Vaccine Failure?

The Council for International Organizations of Medical Sciences (CIOMS), published a 2012 report entitled "The Definition and Application of Terms for Vaccine Pharmacovigilance: Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance [3]. In this report, an attempt was made to define categories of vaccine failure, including "confirmed clinical vaccine failure," "suspected clinical vaccine failure," "confirmed immunological vaccine failure," and "suspected immunological vaccine failure." (See Table 2) This effort is well-meaning and an excellent starting point to encourage more research and thoughtful discussion on how best, in a practical way amenable to today's clinical practice environment, to capture and report vaccine failure.

Thus, an appropriate initial question in the investigation of presumed vaccine failure is the question "is this actually vaccine failure?" For influenza vaccine as an example, I propose a more rigorous definition of vaccine failure as the receipt of a properly stored and administered licensed influenza vaccine to an individual who develops documented influenza after exposure to viruses represented within the vaccine. Documentation of vaccine receipt and an assay documenting infection must be present to fully support the claim of vaccine failure.

It is important to note that inactivated parenterally administered influenza vaccines are designed to result in immune responses that prevent symptomatic illness as well as extensive viral replication and its subsequent complications (e.g., pneumonia, hospitalization, and death). Thus, a vaccine end-point must be specified (i.e. prevention of disease, prevention of a complication, achievement of a correlate of protection, medically attended illness, etc.).

Mechanisms whereby influenza can occur despite immunization include host, vaccine, pathogen, and study-design factors as explored briefly below (Table 3).

3. Host Factors

Like other factors explored below, host factors represent secondary issues that revolve around other mechanisms that can result in vaccine failure. Optimal vaccine immunogenicity occurs when the host is healthy with highly functioning innate, adaptive humoral, and cellular immune systems intact. Multiple factors can impair these immune mechanisms; immunosuppressing medications and therapies, obesity, stress levels [4], levels of fitness [5], and others have been shown to depress the immune response to influenza vaccine. Other factors that can impair immunogenicity include the following:

3.1 Immunoimmaturity or Immunosenescence.

Infants and the elderly do not respond as well to influenza vaccines as those persons in the broad middle of the age spectrum. Between the ages of 6 months and 9 years, children must receive two doses of seasonal influenza vaccine in the year that they receive influenza vaccine for the first time in their lives. Immune responses to influenza vaccine also decline among older adults. For this reason, new vaccines have been developed, including a vaccine providing four-fold the antigen dose for each strain, and a recently licensed vaccine adjuvanted with MF59—both recommended for use in persons age 65 and older.

3.2 Immunocompromise.

Immunocompromising medical conditions (e.g., diabetes, obesity, HIV infection, cancers, a variety of other diseases) and their associated therapies can lead to insufficient or absent immune responses to vaccines. Chemotherapeutic and immune-modifying drugs commonly interfere with response to influenza vaccines. While influenza vaccines are still generally recommended in these cases (with the exception of live viral vaccines), vaccination is done so on the precautionary principle that at least some level of immune response/protection may occur, and it seems appropriate when the documented risks of serious adverse events due to influenza vaccines are almost immeasurably low, while the risks of influenza infection are much higher.

3.3 Genetic Restriction of Vaccine Response.

We and others have documented that specific genetic polymorphisms in HLA, cytokine gene, and cytokine receptor genes result in dampened innate and adaptive immune responses to influenza vaccine[6]. In addition, gender-based differences in vaccine immune responses occur [7]; however, in the latter case it is unclear if this results in differential efficacy.

3.4 Negative Interference.

Some studies have suggested that repeated homologous annual influenza vaccination with the same vaccine in the face of increasing antigenic distance between an epidemic strain and the original vaccine strain can lead to lower antibody levels and increased rates of vaccine failure. This has been called the “antigenic distance hypothesis,” and may—in combination with the phenomenon of original antigenic sin (the observation that prior exposure to a

specific antigen leads to a suboptimal immune response to a later closely related antigen)—be an important and underappreciated factor in vaccine failure rates [8, 9].

3.5 Waning of Antibody Levels.

Influenza vaccine-induced antibody levels gradually wane over time, in some cases by as much as two-fold over a 6-month time period, especially if peak titers are low to begin with [10]. We and others have demonstrated that antibody titers can wane quickly in subsets of subjects;[11] therefore, low post-vaccination titers could wane to non-protective levels and result in disease upon viral exposure later in the influenza season. This may particularly be an issue among the elderly and those with less than optimal immune system function, as has been demonstrated.[12]

3.6 Humoral vs. Cellular Immunity.

Humoral immunity (hemagglutinin inhibition antibody – HAI) is most often used as a correlate of protection against influenza; however, it is imperfect and no level of antibody provides absolute immune protection. Cellular immune responses have been demonstrated to be important in protection from influenza, and current inactivated split virus vaccines do not stimulate high levels of cellular immunity [13]. Cytotoxic T-cell immunity is also more broadly cross-reactive against related influenza strains compared to humoral immunity [14]. The optimal levels and balance between these arms of immunity is unknown in the case of influenza prevention.

3.7 Prior Exposure and Infection.

Vaccine effectiveness estimates also vary based on age, which is a proxy both for immune system function and prior history of influenza infection, as well as prior influenza vaccination history. Because of their complexity, such factors are difficult to predict and assess, and generally have not been considered in VE studies. Nonetheless, prior influenza virus infection and influenza vaccination impact levels, affinity, and avidity of influenza antibodies, and therefore influence rates of effectiveness and efficacy.

4. Vaccine Factors

4.1 Failure to Store and Handle Vaccine Properly.

Investigation into how closely office practices (where the majority of influenza vaccines are still administered) follow vaccine storage and handling recommendations reveals serious deficiencies [15]. In a recent study of office storage of pertussis vaccines, 76% of pertussis-containing vaccines were stored improperly and resulted in freezing or heating of vaccine [15]. When influenza vaccine freezes, or exceeds storage temperatures above 8 degrees Centigrade for significant periods of time, reduced immunogenicity and vaccine efficacy/effectiveness is likely to result. Improper storage that reduces or inactivates vaccine immunogenicity does not mean the vaccine *itself* has failed, even though the vaccine may otherwise be administered appropriately and disease still results.

4.2 Failure to Administer Vaccine Properly.

Patients often describe unusual methods by which they receive influenza vaccines, including non-approved methods such as dividing the influenza vaccine into two or three separate injections, administration of vaccines not approved for intradermal injection intradermally, and many other off-label and unapproved methods. Some of these may indeed result in some level of vaccine immunogenicity; however, they have either not been studied for efficacy, or have been studied and found to be inferior or ineffective compared to intramuscular administration. Our own studies have demonstrated that using too short a needle for vaccine administration results in injection into the deltoid fat pad, rather than an intramuscular injection, which may result in possible suboptimal immunogenicity [16, 17].

4.3 Non-protective Immune Responses.

Even in an otherwise healthy individual, influenza vaccines can fail to protect against influenza illness. This may occur due to induction of antibody that is non- or sub-protective, of low affinity and avidity, or that results in the generation of antibody to antigens non-critical to protection, and can tie-in with 4.4 below. In an otherwise normal host, this constitutes vaccine failure.

4.4 Antigenic Differences Due to Egg Passage.

Influenza strains closely related to circulating epidemic strains are chosen for vaccine production each year. These strains are adapted, by serial embryonated chicken egg passage, to replicate well in eggs for subsequent vaccine production. This process can result in critical amino acid substitutions in which key antigens can differ between vaccine and epidemic strains that can negatively impact the antigenicity and immunogenicity of the vaccine.[17] For example, Zost et al., in a 2017 PNAS paper demonstrated that the site B HA T160 HA glycosylation mutation was missing in the 2016–2017 egg-propagated vaccine strain, and present in the circulating wild virus strain.[18] The result of this change was that both ferrets and humans who were exposed to the egg-adapted A/H3N2 vaccine strain produced poorly neutralizing antibodies to the A/H3N2 viruses that circulated that season. Production methods that eliminate the need for egg cultivation may mitigate this problem, and several influenza vaccine manufacturers have pursued research in this area – resulting in two vaccines available in the US that do not require egg adaptation of the virus. In the best study that examined this issue in terms of practical outcomes, a recombinant HA vaccine (which retains the T160 HA glycosylation) was superior to egg-adapted and passaged H3N2 virus and the observed probability of influenza-like illness was 30% lower in subjects who received recombinant vaccine than in subjects who received inactivated influenza vaccine ($p=0.006$).[19] Thus, the lower efficacy of egg-adapted vaccine viruses may have been due to additional mutations or changes in the A/Texas/50/2014 vaccine virus. Such issues can and do lead to vaccine failure.

4.5 Time-Mediated Vaccine Failure.

After administration of influenza vaccine in adults (and after the second dose in children), approximately 14 days is required before antibody levels generally reach a peak protective titer. If the time interval between vaccine administration, exposure to the influenza virus, and

the development of symptoms is within this two-week timeframe, it is unreasonable to claim vaccine failure per se, as opposed to failure to allow time for vaccine-induced antibody production.

4.6 Vaccine Type.

Vaccine effectiveness can also vary by vaccine type – an issue just beginning to emerge as an important variable. In a 2015 study examining live versus inactivated influenza vaccines, Zimmerman et al. demonstrated an overall adjusted VE against B/Yamagata of 40% (−20–70%) for inactivated influenza vaccine (IIV), and 74% (25–91%) for live attenuated influenza vaccine (LAIV).[20] However in a 2017 paper, Jackson et al. demonstrated that influenza VE among children 2 to 17 years of age against A/H1N1(pdm09) was 60% (45–75%) for inactivated vaccine, versus −19% (−113–33%) for live attenuated vaccine.[21]

5. Pathogen Factors

5.1 Apparent, But False, Vaccine Failure.

Each year the composition of the influenza vaccine is determined months in advance, allowing time for vaccine manufacture and distribution. This has led to incorrect choices for the B strain about 50% of the time. Is this vaccine failure? I would argue not, in the sense that the vaccine does not contain—nor was it designed to prevent—strains not included in the vaccine.

In addition, there are varying degrees of antigenic distance between circulating strains of influenza. As has been demonstrated in previous A/H3N2 seasons, hemagglutinin inhibition antibody (often used to determine the degree of “match” between vaccine and circulating strains) may not distinguish between viral variants that are antigenically different, causing failures that are reported as influenza A/H3N2 [22, 23]. Further, vaccine efficacy/effectiveness estimates are critically dependent upon the antigenic distance between vaccine strains and circulating viral variants [24].

Antigenic drift, particularly within the viral hemagglutinin protein (the viral receptor-binding protein) within the same influenza season, is a particularly vexing issue for H3N2 viruses as they evolve more rapidly than other strains. This is likely the primary reason for true vaccine failure in otherwise healthy individuals who received properly stored and administered influenza vaccine.

As an example, a case control study of the 2012/13 vaccine against influenza A/H3N2 vaccine in Denmark in persons >65 y/o was performed. Greater than 80% of circulating virus in Denmark at that time was influenza A/H3N2. Vaccine efficacy against laboratory confirmed influenza was estimated at −11% (95% CI −41%–14%) for influenza A/H3N2 and 69% (95% CI = 26%–87%) for influenza B [25]. Antigenic drift was demonstrated to be the etiology of poor vaccine efficacy as sequencing of viral specimens revealed seven amino acid substitutions at key antigenic sites, with four or more substitutions in two or more antibody binding sites that led to an antigenically different virus. One of these, substitutions in the 140–146 region of the HA antigenic site A is characteristic for antigenically distant viruses of epidemic significance.

Additionally, patients often complain the influenza vaccine didn't work because they developed any of a host of symptoms, including "common cold" symptoms, sore throat, cough, nausea, diarrhea, or other symptoms. These are commonly reported as "the flu," but are more likely caused by a rhinovirus, norovirus, or infection other than the influenza virus. Indeed, the co-circulation, and subsequent co-infection with influenza and other respiratory viruses, can lead to increased symptomatic respiratory illnesses driving increased medically attended medical visits – a common outcome used in influenza vaccine effectiveness studies.

5.2 Viral Evasion Mechanisms.

Influenza viruses have developed decoy mechanisms to evade host immune responses, even if influenza vaccine raises protective antibody titers. As one example, the NS1 influenza viral protein has been demonstrated to inhibit the generation of innate and adaptive immune responses by preventing type I interferon release and the induction of protective T-cell responses.[26] Other mechanisms are also possible and *in toto* would constitute vaccine failure.

6. Vaccine Efficacy/Effectiveness Study Factors

Notably, influenza vaccine effectiveness and efficacy vary by season, and hence it is not possible to derive a single overall measure of vaccine failure (or efficacy) across time. When an influenza vaccine is reported as 62% effective, a variety of study-related factors will have influenced this estimate. These include the following:

6.1 Geographic Factors.

Studies have revealed differential vaccine efficacy/effectiveness estimates based on geographic differences that may result in fewer (or more) influenza cases in the same season. Differences in population nutrition and health, differential viral transmission rates, different circulating influenza viral clades, and other factors are among the reasons widely varying efficacy/effectiveness rates are observed using the same vaccine within the same season, but in different geographic locations within the same country. Therefore, vaccine effectiveness estimates in one geographic area may or may not represent reasonable estimates in other geographic areas.

6.2 Study Design and Outcomes.

Varying study designs identify differential qualities of vaccine effectiveness and efficacy, defined as observational trials and randomized controlled trials, respectively. In addition, depending upon the sensitivity and specificity of the laboratory assay used to determine influenza infection, differential "vaccine failure" rates will result. One study found that for every 1% decrease in diagnostic assay specificity for influenza virus infection, vaccine effectiveness was underestimated by 4% [27].

Studies with insufficient subject numbers may result in the inability to confidently claim efficacy/effectiveness. Different study outcomes such as "influenza-like illness" (ILI), laboratory-confirmed illness, acute respiratory illness, pneumonia or hospitalization, and other outcomes are often used. This results in different estimates of vaccine effectiveness. In

one study of adults, inactivated influenza vaccine was 86% effective against laboratory-confirmed influenza, yet only 10% effective when the outcome was all respiratory illnesses [28]. Studies without laboratory-confirmed outcomes (such as the commonly used ILI) are highly influenced by the percentage of the outcome actually due to influenza, and can lead to very misleading reports of vaccine efficacy/effectiveness. In addition, study biases (e.g., selection, information, confounding biases) can hamper and distort estimates of vaccine efficacy/effectiveness, resulting in erroneous estimates of vaccine failure. Finally, one paper demonstrated that in VE case-control studies using test negative control subjects (subjects who were ill and presented for medical care, but were test negative for influenza) vs. traditional control subjects (those who were asymptomatic from the population), consistently led to higher VE estimates among test-negative study designs.[29] For example, in the 2006–2007 influenza season, the adjusted influenza VE using test-negative controls was 52% (22–70%), versus 37% (−10–64%) using traditional control subjects. Such studies illustrate the critical effect that study design may have on influenza VE study estimates.

7. Conclusion

While imperfect, influenza vaccines are a critical part of the influenza-prevention armamentarium. Unfortunately, physicians, nurses, pharmacists, the media, and others commonly use the term “vaccine failure” without understanding the circumstances under which a vaccine did or did not fail in what it is expected to do. This can lead to false claims of “vaccine failure,” increased mistrust in influenza vaccines, and a bias against receiving vaccine. Influenza vaccine can only provide maximum protection to the extent that the circulating and vaccine strains closely match; the vaccine is stored, handled, and administered properly and within a time frame that results in protective levels of immunity; and is administered to an immunocompetent host in which genetic restriction does not prevent development of protective immune responses. In addition, development and use of a proper framework and nosology for describing and identifying vaccine failure can assist in efforts to study and identify actual mechanisms of documented vaccine failure that may be amenable to improvement.

In addition, vaccine effectiveness is dynamic - not a static measure – even within the same influenza season, with multiple variables to consider as noted above. For this reason, single point estimates of VE are moderately unhelpful in that they are incomplete, and obscure important information and caveats. Thus, measures of influenza vaccine effectiveness need to be more nuanced, and effectiveness rates measured throughout the season, for each vaccine component, for each major age group, with simultaneous data on circulating wild virus types. A simple “30% effective” is a population-level estimate (with all its limitations), that offers little actionable information. In addition it is simply insufficient to give such an estimate absent appending which vaccine strain is being discussed, and for what age group.

Vaccines are much like seatbelts or airbags in cars. Maximum protection against injury or death occurs when they are used properly and in the right setting, but they are no guarantee of *absolute* protection and safety. Yet, who wants to be involved in an automobile crash without them? While imperfect, they nonetheless offer the best protection available against serious injury and death. Used properly and in the right setting where the right patient gets

the right vaccine at the right dose, and administered in the right manner, influenza vaccines offer protection against infection, and the complications of infection should it occur. Studies document that influenza vaccines can lower the risk of serious complications, hospitalization, and death—although at differential rates based on the host and other factors discussed above. Improved study designs and specificity of study outcomes are needed, as is the pressing need for resources to conduct these seasonal studies and the need to devise better vaccines with superior immunogenicity and efficacy. So-called "universal" vaccines and newer vaccine adjuvants may be part of this answer. Until then, however, the benefits of current influenza vaccines vastly exceed any known risks, and should be routinely used as a critical part of influenza prevention [30].

8. Expert Commentary

The nosology for vaccine failure is incomplete and inadequately developed. The 2012 Council for International Organizations of Medical Sciences (CIOMS), report on "The Definition and Application of Terms for Vaccine Pharmacovigilance: Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance [3] is a good start. Further work is needed; ideally, a consensus must emerge on categories, definitions, and examples of vaccine vs. non-vaccine failure. This is an important first step toward adequately studying, distinguishing, and cataloging real versus suspected vaccine failure. In turn, such accuracy lends increased credence to reports of true vaccine failure, prevents confusion and misinterpretation of reported vaccine failure, and may serve to either increase confidence in vaccines or suggest and motivate vaccine developers toward areas for further research and/or avenues for new vaccine research and development. For example, validated data demonstrating true vaccine failure and its root cause(s) is important to directing additional research to understand the mechanistic basis of vaccine failure. In turn, the results of such research are highly likely to inform and motivate new *directed* vaccine-development efforts toward a more highly immunogenic/efficacious vaccine. With the advent of increasingly high-dimensional systems biology and vaccinomics approaches to understanding the development of immunity after vaccination [31, 32], as well as the discovery of molecular signatures and biomarkers for vaccine immunogenicity, such research will be enabled.

Additional practical, or clinical, reasons also exist for a proper nosology. Clinicians need an algorithm or template that they can use to determine and report real or possible causes of vaccine failure. For example, any vaccine adverse event may be reported through the Vaccine Adverse Events Reporting System (VAERS). Enhancing the system to explicitly request reporting for vaccine failure as a type of adverse event would be a valuable research tool, and would give more population-level data as to particular situations or sub-groups experiencing vaccine failure.

9. Five Year View:

Over the next five years, it is highly likely that improved influenza vaccines will be available. Such is already the case for immunosenescent individuals. The development of newer vaccines will be motivated by issues of poor vaccine effectiveness and efficacy among current vaccines. Mammalian cell-adapted—versus egg-adapted—vaccine viruses may be

one pathway toward improving vaccine effectiveness. Regardless, clear and well thought out algorithms are needed—and healthcare providers instructed—on the definitions of true vs. false vaccine failure. It is likely that enhanced surveillance studies and efforts will be developed to better monitor real world (as opposed to carefully constituted clinical trials) vaccine efficacy. The 2012 CIOMS report is a good start; perhaps it will spark additional research and discussion, evolving into a more explicit and regularly utilized mechanism for understanding and reporting vaccine failure.

10. Key Issues:

1. Influenza vaccine failure is defined as receipt of a properly stored and administered vaccine with the subsequent development of documented influenza. Several mechanisms of vaccine failure occur and can—either alone, or in combination—lead to what is termed “vaccine failure.”
2. Influenza vaccine can only provide maximum protection to the extent that the circulating and vaccine strains closely match; the vaccine is stored, handled and administered properly and within a time frame that results in the development of protective levels of immunity; and is administered to a host capable of immunologically responding with protective immune responses.
3. How we define the term “vaccine failure” has tremendous implications for how we study and measure vaccine failure; how we interpret the results of those studies; how we report it to the public, health professionals, and the media; how we formulate public policy as a result of such study findings; and how it eventually impacts vaccine uptake and health care costs.
4. A consensus must emerge on categories, definitions, and examples of vaccine vs. non-vaccine failure. This is an important first step toward adequately studying, distinguishing, and cataloging real, suspected, and putative vaccine failure.

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A reviewer on the manuscript has disclosed receipt of research funding from Merck & Co., Inc. and Pfizer Inc. Another reviewer disclosed employment with Sanofi Pasteur, which manufacturers influenza vaccine. In the manuscript, there was specific reference to at least 2 of the influenza vaccines that Sanofi Pasteur manufactures.

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Table 1.

Vaccine Effectiveness Estimates By Season

Season	Number of Subjects[+]	Adjusted VE (95% CI)	Reference
2004–2005	762	10 (−36,40)	[29]
2005–2006	346	21 (−52,59)	[29]
2006–2007	871	52 (22,70)	[29]
2007–2008	1,914	37 (22,49)	[33]
2008–2009	6,713	41 (30,50)	Unpublished
2009–2010	6,757	56 (23,75)	[34]
2010–2011	4,757	60 (53,66)	[35]
2011–2012	4,771	47 (36,56)	[36]
2012–2013	6,452	49 (43,55)	[37]
2013–2014	5,999	52 (44,59)	[38]
2014–2015	9,311	19 (10,27)	[20]
2015–2016[*]	6,879	48[*] (41,55[*])	[21]
2016–2017[**]	7,410	39[**] (32,46)	Unpublished final estimates.

[*] Estimate from November 2, 2015 – April 15, 2016

[**] Interim 2016–2017 VE estimates (April 20, 2016 – April 9, 2017)

[+] Number of patients used in VE estimate

Table adapted from reference 1 - Centers for Disease Control and Prevention. Seasonal Influenza Vaccine Effectiveness, 2005–2018.

Table 2.

Definitions of Vaccine Failure

Confirmed clinical vaccine failure	The occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunization. The application of this definition requires clinical and laboratory confirmation (or epidemiological link to a confirmed case, where applicable) that the actual disease is vaccine preventable, i.e. that the pathogen (including, where appropriate, type, subtype, variant, etc.) and clinical manifestations are specifically targeted by the vaccine.
Suspected clinical vaccine failure	The occurrence of disease in an appropriately and fully vaccinated person, but the disease is not confirmed to be the specific vaccine-preventable disease, e.g. invasive pneumococcal disease of unknown serotype in a fully vaccinated person. Applying this definition also requires that the incubation period and the normal delay for the protection to be acquired as a result of immunization have been taken into account.
Confirmed immunological vaccine failure	The failure of the vaccinee to develop the accepted marker of protective immune response after being fully and appropriately vaccinated. This definition requires that there is an accepted correlate or marker for protection, and that the vaccinee has been tested or examined at an appropriate time interval after completion of immunization.
Suspected immunological vaccine failure	The same definition as above except that the time-frame for testing after immunization may be inappropriate and therefore it is difficult to assess vaccine failure.

Definitions taken verbatim from CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Definition and Application of Terms for Vaccine Pharmacovigilance. http://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf. 2011. Date accessed: November 28, 2017.”

Table 3.

Factors Impacting Vaccine Failure

Pathogen Factors	• Antigenic drift/distance between vaccine and circulating strains • Co-infections—interference • Viral decoy mechanisms • Viral immune evasion mechanisms
Host Factors	• Immunocompromised • Co-morbidities • Age/immunosenescence • Obesity • Genetic restriction • Medications • Negative interference • Role of humoral vs. cellular immunity • Waning immunity • Pre-existing infection • Immunologic interference
Vaccine Factors	• Improper administration • Differences in immunogenicity (adjuvanted vs. non-adjuvanted) • Dosage and number of doses • Time between vaccination and development of immunity • Egg-passage-induced antigenic changes in vaccine • Handling • Temperature inactivation • Vaccine-vaccine interference
Study/Study Design Factors	• Geography • Confounding biases • Efficacy vs. effectiveness • Prevalence of infection • Study design • Specificity of study outcomes • Year of study • Laboratory assays used • Incubation period vs. timing of immunization

Table Adapted from CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Definition and Application of Terms for Vaccine Pharmacovigilance. http://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf. 2011. Date accessed: November 28, 2017."