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Evaluating the Target-Population Recommendations for Influenza Vaccination: Evidence and Ethics

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Evaluating the Target-Population Recommendations for Influenza Vaccination: Evidence and Ethics

by

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas Medical Branch

in Partial Fulfillment

of the Requirements

for the Degree of

Doctorate of Philosophy

The University of Texas Medical Branch

November 2016

Dedication

This dissertation is lovingly dedicated to the man who inspired me to try and change the world for the better. Who never questioned my ability (even as a small, annoying child) to be a lawyer, doctor, and a chef, at the same time. Who never doubted that I could do anything, even when I doubted myself.

In loving memory of William Carson

January 31, 1949 – October 6, 1997

Always.

Acknowledgments

This dissertation would not have been completed without the support of the following people:

My committee, Dr. Cheryl Vaiani, Dr. Alan Barrett, Dr. Cheryl Erwin, Dr. Michele Carter, and Dr. Bernadette McKinney, Thank you for your mentorship and support through this process.

Dr. Justin Ortiz, WHO Initiative for Vaccine Research, Thank you for guiding the developing of the systematic review that led to this dissertation.

The Sealy Center for Vaccine Development, for providing and funding the internship that led to this dissertation.

Dr. Anne Hudson Jones, Medical Humanities Graduate Program Director. Thank you for your time and dedication in getting both this proposal and project on track.

Donna Vickers, Former Medical Humanities Graduate Program Coordinator, Thank you for all the time you took to keep me on track with the various required paperwork. You were the best graduate school "mom" I could ask for.

Dr. David Niesel, UTMB GSBS Dean, Your mentorship and guidance throughout my time at UTMB has been invaluable. Thank you for convincing me not to drop out.

Zelda Zinn Casper Scholarship Fund, stipend funding for the 2014-2015 academic year.

Tom Lucas, Biochemistry and Molecular Biology Program, editing, tech support, caffeine support, nutritional support, and emotional support.

Evaluating the Target-Population Recommendations for Influenza Vaccination: Evidence and Ethics

Publication No._____

Heather Nicole Carson, Ph.D.

The University of Texas Medical Branch, 2016

Supervisor: Cheryl Ellis Vaiani

The influenza virus infects between 5 and 10 percent of the population each year, resulting in acute respiratory illness ranging from subclinical to severe; during a pandemic, 50 percent of the population can easily be infected. Influenza infection creates serious social, economic, and public health impacts; vaccination is the safest and most effective way to prevent infection and diminish these impacts. While seemingly straightforward, the influenza vaccine manufacturing process is fragile. Vaccine supply may suddenly decrease due to manufacturing issues, or the supply can be nonexistent due to a pandemic requiring the production of a new vaccine. Vaccine scarcity, for either reason, requires the use of target-population recommendations to allocate the vaccine until stocks can be restored. Target-population recommendations reflect the groups at highest risk of developing severe illness and complications from infection with the influenza virus. This project evaluates the target-population recommendations for the influenza vaccine, proposes improvements to facilitate evidence-based policymaking, and determines the ethical framework guiding the recommendations. This project utilizes methods from the humanities the disciplines of history, ethics, philosophy, and law are used in conversation with the scientific review. The central finding of this project is that adapting the current methodology used to evaluate influenza research would lead to better recommendations and contribute to improved communication between key stakeholders.

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UTMB	University of Texas Medical Branch
GSBS	Graduate School of Biomedical Science
WHO	World Health Organization
CDC	Centers for Disease Control and Prevention

Overview

The influenza virus infects between 5 and 10 percent of the world's population each year creating serious social, economic, and public health impacts.[1] Vaccination is the safest and most effective way to prevent infection and diminish these impacts. Ideally, everyone without a contraindication to the vaccine would be willing and able to receive an influenza vaccination. Due to the consistent evolution of the influenza virus, a new vaccine is required each season. The requirement for a new vaccine each season combined with the vaccine manufacturing process can result in a vaccine shortage. Vaccine shortages can also be the result of an influenza pandemic requiring a new vaccine to be developed. Although 400 million doses of the influenza vaccine are produced each ear, more than any other vaccine, any increase in demand or vaccine shortage requires an allocation plan.[2] Target-population recommendations are used to assist with vaccine allocation.

Target-population recommendations identify the groups considered to be at highest risk of suffering severe illness, complications, or death from infection with the influenza virus. Identifying and vaccinating groups at higher risks of severe illness is the more appropriate vaccination strategy because unlike smallpox and polio the influenza virus cannot be eradicated via vaccination. The goal of vaccination is to reduce the number of lives lost and the overall burden of influenza infection; target-population recommendations address this goal in the most rational manner. The World Health

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[1] World Health Organization, "Influenza Vaccines WHO Position Paper," *Weekly Epidemiological Record* 80, no. 33 (August 19, 2005): 277-88.

[2] Alan Barrett, personal communication to author, September 19, 2016.

Organization (WHO) and the Centers for Disease Control and Prevention (CDC) both issue target-population recommendations for the influenza vaccine.[3] The Centers for Disease Control and Prevention have recommended the seasonal influenza vaccine since 1960.[4] In the United States, the target-population recommendations set the policy for insurance reimbursement, as well as guide state and local vaccination programs. The World Health Organization began publishing policy positions on influenza vaccinations as a part of the Global Agenda on Influenza.[5] The Global Agenda on Influenza was adopted in 2002 to outline activities "critical to mobilizing action to reduce morbidity and mortality due to annual influenza epidemics and prepare for the next influenza pandemic."[6] These policy positions are meant to encourage countries to establish national policies and set immunization targets.[7] Both the WHO and CDC have guidelines in place to support the development of evidence-based recommendations, but a systematic investigation of the evidence used to develop the target-population recommendations has not been completed.[8] **This project seeks to evaluate the evolution of the target-population recommendations and propose changes to facilitate improvement to evidence-based influenza policy.** The evaluation and proposed changes will determine if

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[3] Other countries issue vaccination recommendations; however, the recommendations of the WHO and CDC will be the focus of this project.

[4] Leroy E. Burney, "Influenza Immunization: Statement," *Public Health Reports* 75, no. 10 (October 1960): 944. These initial recommendations were in response to the 1957 Avian Influenza Pandemic and defined specific populations to receive the seasonal vaccine for the first time.

[5] World Health Organization, "Adoption of Global Agenda on Influenza-part II," *Weekly Epidemiological Record* 77, no. 23 (June 7, 2002): 191-196, 191.

[6] Ibid., 191.

[7] Ibid., 193.

[8] There have been articles criticizing the WHO recommendations but the two recommendations have not been considered jointly.

the target-population recommendations are based on the best available evidence and if there is a way to improve the recommendations.

DESCRIPTION OF THE DISEASE AND THE INTERVENTION

Influenza is a member of the *Orthomyxoviridae* family and possesses six to eight chains of RNA.[9] There are three types of influenza strains: A, B, and C. Influenza A causes infection in humans, other mammals, and fowl.[10] The influenza virus is believed to have originally been avian before making the jump to humans.[11] Birds are major reservoirs for all strains of influenza A, but only H1, H2, H3, N1, and N2 are currently prevalent in humans.[12] Influenza B is only known to infect humans, has slower rates of change and causes milder illness compared to Influenza A.[13] Influenza C infects humans and swine but is rare and mild in humans with fewer than a dozen cases being reported.[14] The influenza virus is classified based on the surface antigens; hemagglutinin, of which there are sixteen, and neuraminidase, of which there are nine.[15]

Influenza infection causes acute febrile respiratory illness that ranges in severity from subclinical to fatal. Influenza is highly contagious via aerosolized droplets and

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[9] James W. Brasseur, "Pandemic Influenza: A Brief History and Primer," *Journal of the American Academy of Physician's Assistants* 20, no. 1 (January 2007): 24-28, 25.

[10] Ibid.

[11] Ibid.; Robert G. Webster, "Influenza: An Emerging Microbial Pathogen," In Emerging Infections edited by Richard M. Krause, *Biomedical Research Reports* 275-300, 251. Cambridge Massachusetts: Elsevier 1998.

[12] Yu-Chia Hseih, et al., "Influenza Pandemics: Past, Present and Future," *Journal of the Formosan Medical Association* 105, no. 1 (January 2006): 1-6.

[13] Brasseur, "Pandemic Influenza" 25.

[14] Brasseur, "Pandemic Influenza" 25.; Webster, "Influenza: An Emerging Microbial Pathogen," 281.

[15] Kristen Kuszewski, and Lidia Brydak, "The Epidemiology and History of Influenza," *Biomedicine & Pharmacotherapy* 54, no. 4 (May 2000): 188-95, 188.; Richard J. Webby, and Matthew Robert Sandbulte, "Influenza Vaccines," *Frontiers in Bioscience* (May 1, 2008): 4912-4924, 4913.

contaminated surfaces.[16] The highest rates of severe illness and death from seasonal influenza occur in populations over the age of sixty-five, under the age of two, and in people with comorbid medical conditions.[17] These populations compose the target-populations for vaccination. Pandemic influenza has unpredictable attack patterns and mortality rates. Symptoms of influenza infection can include "fever, cough, sore throat, runny nose, headache, muscle and joint pain, and severe malaise," although not all infected persons exhibit all symptoms.[18] Influenza infection can also cause complications including "bacterial pneumonia, ear infections, sinus infections, dehydration," and exacerbation of underlying medical conditions, particularly cardiac and pulmonary conditions.[19] Deaths resulting from influenza complications, such as bacterial pneumonia or exacerbation of underlying disease, are often inaccurately reporting, making the burden of influenza infection difficult to accurately quantify.

The influenza vaccine was created in 1936 and became commercially available in 1945.[20] The influenza vaccine work by eliciting a strain-specific immune response and are recommended annually due to changes in the circulating virus. The influenza vaccine is manufactured in a four-part process involving the use of eggs:[21]

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[16] Robert J. Pratt, "The Global Swine Flu Pandemic 1: Exploring the Background to Influenza Viruses," *Nursing Times* 105, no. 34 (September 1, 2009): 18-21.

[17] Anthony Fiore et al., "Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009," *Morbidity and Mortality Weekly Report* 58, no. RR-8 (July 31, 2009): 1-52.

[18] Michael T. Osterholm, Nicholas S. Kelley, Alfred Sommer, and Edward A. Belongia, "Efficacy and Effectiveness of Influenza Vaccines: A Systematic Review and Meta-Analysis," *Lancet Infectious Disease* 12, no. 1 (January 2012): 36-44.

[19] Nancy J. Cox, "Prevention and Control of Influenza," *Lancet* 354, Special Issue (December 1999): SIV30.

[20] Richard J. Webby, and Matthew Robert Sandbulte, "Influenza Vaccines," *Frontiers in Bioscience* (May 1, 2008): 4912-4924, 4913.

[21] This process is further discussed in chapter one and can only begin after the virus strains are selected, and the candidate strains are grown, and shipped to the manufacturer.

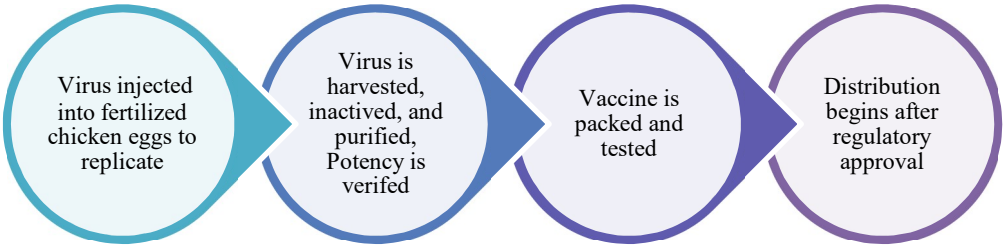

FIGURE 1: SIMPLIFIED INFLUENZA VACCINE PRODUCTION PROCESS

The seasonal influenza vaccine is available in trivalent (protection against three virus strains) and quadrivalent (protection against four virus strains) formulations. During a pandemic, a monovalent vaccine may also be used. While seemingly straightforward, the influenza vaccine manufacturing process is fragile. Vaccine supply may suddenly decrease due to manufacturing issues, or the supply can be non-existent due to a pandemic requiring the production of a new vaccine. Vaccine scarcity, for either reason, requires distribution of available supplies to be done via an allocation plan until stocks can be restored. Focusing vaccination efforts and supplies on those most likely to suffer severe illness allows the social, economic and public health burdens of the influenza virus, which cannot be eradicated, to be managed most effectively.

PROJECT AIMS

The goal of this project is to evaluate and recommend improvement to influenza vaccine policy. Influenza vaccine policy needs to be evaluated and improved because of the misconceptions regarding the virus, the vaccine, and the current policy. This project will utilize the lenses of science, history, ethics, and policy to evaluate the research that

informs the target-population recommendations for influenza vaccination and develop a proposal to improve evidence-based policymaking. These objectives will be fulfilled by the completion of the following three aims. Aim one is to **analyze the current research evaluation methodologies to assess the application to the evidence base for target-population recommendations.** This aim will require the additional analysis of the types of research used to support the target-population recommendations. Aim two is to **develop recommendations to improve evidence-based policymaking for influenza vaccine policy.** This aim will be supported by an evaluation of general policymaking procedures in comparison to the evidence-based policymaking process. The final aim is the **development an ethical justification to support the use of target-population recommendation for influenza vaccines.** This aim will require the analysis of the ethical framework guiding the creation of target-population recommendation in the event of a pandemic.

SIGNIFICANCE

Target-population recommendations are significant for two main reasons. First, target-populations receive de facto priority even when a vaccine shortage does not exist. This de facto priority is created through population-specific vaccination initiatives and increased communication to both the public and healthcare providers regarding the importance of vaccination to these groups. This means that people outside of the target-populations may not be offered the influenza vaccine as frequently nor are they well informed about the benefits of receiving the vaccine. Lack of offers to vaccinate and information on the benefits of vaccination contributes to low vaccine coverage levels and missed vaccination opportunities. Target-population recommendations become priorities

during a vaccine shortage. Unless these recommendations are supported by high-quality research, prioritization can exacerbate the socioeconomic and public health impacts of influenza infection that vaccination is intended to prevent. Target-population recommendation should be evidence-based with a solid ethical framework and presented in a clear, concise manner that is accessible to all audiences.

METHODS

This project combines science, policy, and ethics to evaluate influenza vaccination policy with the purpose of improving existing processes to promote just policy, quality research, and better health. As such, this work is well located within the field of the medical humanities. The medical humanities exist at the intersection of science and the humanistic disciplines, integrating the fields of collaborative inquiry to increase health and well-being of the individual and society as a whole.[22]

In this project methods from the humanities, disciplines of history, ethics, philosophy, and law are used in conversation with the scientific review. The influenza pandemics from 1900 to 2009 will be used to illustrate the human experience and societal burden of influenza infection. Additionally, the discovery of the influenza virus and vaccine will be discussed linking the scientific background with the historical narrative. Philosophy is a central theme of this project through the exploration of classical rhetoric, the ethical principle of justice, and the ethical theory of utilitarianism. One of the goals of

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[22] Thomas Cole, Nathan Carlin, and Ronald Carson, *Medical Humanities: An Introduction.* New York, NY: Cambridge University Press, 2015.; H.M. Evans, and J. Macnaughton, "Should Medical Humanities Be a Multidisciplinary or an Interdisciplinary Study?" *Journal of Medical Ethics: Medical Humanities* 30 no. 1 (June 2004): 1-4.

this project is to establish both an argument and process for evidence-based policy in regards to influenza vaccinations. Evidence-based policy integrates science and rhetoric with the purpose of creating rules that garner better results, encourage compliance, and bolster public trust in both the policy and the intervention. Science, including public health, links the disciples together and provides the core narrative of the project- that influenza vaccines are important tools in improving health and saving lives thus the policy governing their use and allocation should be based on high-quality clinical research.

PROJECT OUTLINE AND CHAPTER SUMMARY

This project consists of six chapters that develop the foundation, fulfill the stated aims, and conclude with a summary and discussion of future directions.

Chapter one will provide the scientific and historical background of influenza virus and vaccine. This chapter is divided into two main sections. The first section provides the background of influenza virus itself, including the pandemics between 1900 and 2009. The second section discusses the development and manufacturing processes of the influenza vaccine.

In chapter two I will describe the process of policymaking and demonstrate how classical rhetoric can be leveraged to improve evidence-based policymaking for influenza vaccines. My main argument is that the use of rhetorician's skill set may improve meaningful utilization of research in policymaking and improve communication between researchers, policymakers, and the public. Increasing the quality of communication through rhetorical and hermeneutical means may also bolster public trust concerning research and vaccines.

Chapter three will analyze the process of creating the target-population recommendations and evolution of the recommendations over time. The WHO and CDC use strikingly similar processes to determine the target-population recommendations with the main differences being the audience, legislative authority, and the frequency of publication. The differences reflect the level of resources available and epidemiological differences between the CDC and WHO.

Chapter four has three objectives. First, to determine the types of research available and utilized to determine the target-population recommendations. Second, to analyze the available research evaluation methodologies and determine their ability to assess vaccine research. Finally, I will propose improvements to the evaluation methodologies in application to vaccine research.

Chapter five explores the ethical framework for the target-population recommendations. I argue that the target-population recommendations for influenza vaccination are fair and equitable despite the shortcomings in the evidence base for three reasons. First, the target-population recommendations are based on the best evidence currently available and evolve with changes in the evidence. Second, the target-population recommendations can be supported via the ethical theory of utilitarianism. Finally, the target-population recommendations satisfy the principle of justice.

The final chapter provides a summary of the project by highlighting the completion of the aims and exploring future directions.

Chapter 1: Influenza Virus and Vaccine

Influenza virus's ability to continuously evolve by antigenic variation and reasortment, causing annual epidemics and sporadic pandemics thwarts attempts at control. The broad objective of this chapter is to provide the scientific and historical background of influenza virus and vaccine. This chapter is divided into two main sections. The first section provides the background of influenza virus itself, as well as the pandemics between 1900 and 2009. The second section discusses the development and manufacturing processes of the influenza vaccine.

INFLUENZA BACKGROUND

Influenza-like infections have been described throughout history.[23] Hippocrates described an epidemic in 412 B.C.E that has been accepted as one of the first potential influenza epidemics.[24] The medical history community has debated the date of the first confirmed influenza epidemic with some scholars allowing as far back as 827 C.E. and other arguing for sometime between 1173 and 1387 C.E.[25] Scientific and lay literature have made references to influenza-like epidemics since 1650 with evidence supporting ten probable and three possible pandemics since 1590 illustrating the historical frequency and burden of influenza infections.[26] What can be agreed on is that influenza infections

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[23] Influenza-like infections occur when the patient exhibits symptoms of influenza infection, i.e. cough, muscle aches, fever, runny nose, fatigue, but there is no laboratory confirmation of influenza infection.

[24] Kuszewski and Brydak, "The Epidemiology and History of Influenza," 188.

[25] W. I. B. Beveridge, "The Chronical of Influenza Epidemics," *History and Philosophy of the Life Sciences* 13 no. 2 (1991):223-234, 225.

[26] C. W. Potter, "A History of Influenza," *Journal of Applied Microbiology* 91, no. 4 (October 2001): 572-79, 572.

have "been killing people by the thousands at irregular intervals throughout recorded history, and we can still do little to protect the world community."[27]

Influenza virus was successfully isolated in 1933 by Wilson Smith, Sir Christopher Andrewes, and Sir Patrick Laidlaw of the National Institute for Medical Research in London.[28] Briefly, the influenza virus is a member of the *Orthomyxoviridae* family and spherical shaped like a spike globe with two surface proteins, hemagglutinin, and neuraminidase.[29] Despite the eighty- plus years of laboratory experience with influenza, the virus is still considered an major pathogen because the virus continues to evolve new strains.[30] Humans lack immunity to these novel strains creating the potential for epidemics and pandemics. This evolution is due to two processes, antigenic shift and antigenic drift. Antigenic drift is due to errors during RNA replication combined with natural section (selective pressure) resulting in viruses that have mutations in antigenic sites on the hemagglutinin recognized by antibodies such that novel, but similar, forms of the influenza virus are generated.[31] Antigenic drift is one of the reasons a new vaccine is required every year; the changes made during antigenic drift render the prior year's

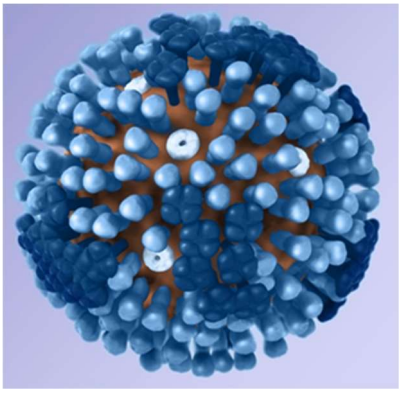

Illustration 1: Influenza Virus Photo Source: CDC Public Health Image Library, ID 11880.

[27] Beveridge, "The Chronical of Influenza Epidemics," 223.
[28] Webster, "Influenza: An Emerging Microbial Pathogen," 270.
[29] Richard J. Webby, and Matthew Robert Sandbulte, "Influenza Vaccines," *Frontiers in Bioscience* (May 1, 2008): 4912-4924, 4913. The influenza virus was additionally described in the overview chapter.
[30] Webster, "Influenza: An Emerging Microbial Pathogen,"275.
[31] Webby, "Influenza Vaccines," 4913.

vaccine ineffective.[32] Antigenic shift occurs much less frequently than drift but results in a more dramatic change of the virus. Antigenic shift occurs when a host is infected with two influenza strains where the eight segments that make up the influenza virus genome shuffle within the infected cell to create a novel pathogen with segments from both infecting viruses; this combination is known as genetic reassortment.[33] These changes can occur using an intermediary, such as swine, or directly in an infected person.[34] Influenza virus strains that cause pandemics emerge from antigenic shift and have several common characteristics: sudden appearance, antigenically distinct from circulating strains, and confined to hemagglutinin H1, H2, and H3 subtypes that readily infect humans.[35] Antigenic shift cause pandemics when the individual has no immunity to the infecting virus and person-to-person transmission is high.[36] Influenza is challenging from a planning and policy standpoint due to its unpredictable nature. Each year new strains pose risks, and the potential for a pandemic is ever present, but there is also the chance that the influenza season will be particularly mild. Thus, the challenge becomes balancing the need for preparedness with avoiding public panic and threat fatigue.[37] This balancing act requires the integration of science, ethics, and public communication in order to craft plans that appropriately address needs on a seasonal level but are also flexible enough to be adapted quickly to pandemic situations. Threat fatigue is particularly dangerous with

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[32] Nancy J. Cox, and Kanta Subbarao,"Influenza," *Lancet* 354, (October 9, 1999):1277-1282, 1277.

[33] Webby, "Influenza Vaccines," 4913; Webster, "Influenza: An Emerging Microbial Pathogen," 279.

[34] Ibid.

[35] Webster, "Influenza: An Emerging Microbial Pathogen," 280.

[36] Cox and Subbarao, "Influenza,"1278.

[37] Threat fatigue occurs when the risk of harm becomes normalized and thus people no longer respond to threats.

influenza because it can contribute to lower yearly vaccination rates; thus increasing the annual burden of influenza. When influenza is not seen as a health concern, people are less likely to be vaccinated even in the event of a pandemic. Researchers and healthcare workers must demonstrate the ongoing value of influenza vaccination during inter-pandemic years to strengthen and maintain the infrastructure for vaccination programs, maintain corporate investment, and public awareness. This demonstration can be made through regular publication of research results if those publications are accessible to health care workers (including physicians), policymakers and the lay public. Accessibility is dependent upon research results being reporting in a manner that is understandable and freely available.[38] Each year approximately 5 to 10 percent of adults and 20 to 30bpercent of children are infected with influenza virus.[39] While 5 to 10 percent may not appear to be a large percentage, the practical impact can be high. The City of Houston has 1,556,427 residents over the age of eighteen; if 8 percent of the population were to contract clinical influenza disease, it would result in 124, 514 cases.[40] This simple equation does not account for the amount of lost work time or the proportion of people who would need to be hospitalized, or the amount of money spent on care, merely the number of cases. Influenza infection creates a yearly economic toll in the United States of approximately 87 billion dollars, including 10 billion dollars in direct medical expenses.[41]

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[38] Accessibility of research to policymakers and the lay public will be further discussed in chapter two.

[39] World Health Organization, "Influenza Vaccines WHO Position Paper," *Weekly Epidemiological Record* 80, no. 33 (August 19, 2005): 277-88.

[40] City of Houston, 2010 Age and Sex City of Houston: Source: 2010 PL94-171 Data, US Census Bureau. City of Houston Planning & Development Department. Accessed January 16, 2016. Available at http://www.houstontx.gov/planning/Demographics/docs_pdfs/Cy/coh_age_sex.pdf.

[41] Noelle-Angelique M. Molinari, et. al., "The Annual Impact of Seasonal Influenza in the Us: Measuring Disease Burden and Costs," *Vaccine* 25, no. 27 (June 28, 2007): 5086-96.

Influenza infection results in a hospitalization rate of 35.5 per 100,000 in the United States.[42] The exact number of deaths caused by influenza each year is difficult to determine because influenza may not be listed as the primary cause of death. Nonetheless it is estimated that influenza is the cause of death for at least three thousand and as high as forty-nine thousand people per year.[43] Despite the high economic and human costs, influenza appears to be disregarded by the general public as non-threatening until there is a threat of a pandemic or a vaccine shortage. Despite the wide availability of the influenza vaccine in the United States, only 59.3 percent of children and 43.6 percent of adults received the influenza vaccine during the 2014-1015 influenza season.[44] The low vaccine demand in non-pandemic years threatens the infrastructure for influenza vaccine delivery as well as the health of those remaining unvaccinated. Low vaccine uptake threatens the infrastructure for influenza vaccine delivery by decreasing the financial incentive for companies to invest in manufacturing, research and development. Additionally, children who are vaccine naive may require two doses for full effect creating additional supply challenges during a shortage.

INFLUENZA PANDEMICS

A pandemic is defined as a widespread epidemic of any disease but often refers to a worldwide epidemic caused by a new subtype of influenza A in the human

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[42] Ernest Milian, and Amine A. Kamen. "Current and Emerging Cell Culture Manufacturing Technologies for Influenza Vaccines," *BioMedical Research International* Volume 2015, Article ID 504831.

[43] Centers for Disease Control and Prevention, Estimating Seasonal Influenza-Associated Deaths in the US: CDC Confirms Variability of the Flu. last modified March 18, 2015. Accessed January 19, 2016, http://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm.

[44] Tammy A. Santibanez et. al., "Flu Vaccination Coverage, United States, 2014-15 Influenza Season | FluVaxView | Seasonal Influenza (Flu) | CDC." Centers for Disease Control and Prevention, Updated January 28, 2016. http://www.cdc.gov/flu/fluvaxview/coverage-1415estimates.htm.

population.[45] To be classified as an influenza pandemic the outbreak must be caused by a new influenza A subtype that is not related to the circulating viruses and could not have arisen via antigenic drift.[46] The WHO currently uses a six-phase approach to describing influenza pandemics.[47] In Phases 1 through 3 there is predominately animal infections with few human infections.[48] When a novel influenza virus has verified human-to-human transmission that causes community-level outbreaks, the Director-General may raise to Phase 4, meaning there is an increase in the risk of a pandemic, but this does not mean that a pandemic is a forgone conclusion.[49] Phase 5 is characterized by human-to-human transmission in at least two countries in one WHO region.[50] Community-level outbreaks in at least two different WHO regions can lead to a Phase 6 designation of a global pandemic.[51] During the post-peak period infection rates have dropped signaling a decrease in pandemic activity, which could precede additional waves of infection.[52] Influenza activity returns to normal seasonal levels during the post-pandemic period.[53] The current WHO approach is only useful for evaluating a pandemic when real-time laboratory surveillance is available and is, therefore, inadequate for historical evaluations. Historical evaluations of influenza pandemics allow for the assessment of the human and social burden of influenza infections over time.

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[45] Youri Ghendon, "Introduction to Pandemic Influenza through History," *European Journal of Epidemiology* 10, no. 4 (August 1994): 451-3, 451.

[46] C. W. Potter, "A History of Influenza," *Journal of Applied Microbiology* 91, no. 4 (October 2001): 572-79, 574.

[47] World Health Organization, "WHO | Current WHO Phase of Pandemic Alert for Pandemic (H1N1) 2009." Accessed March 29, 2016. http://www.who.int/csr/disease/swineflu/phase/en/.

[48] Ibid.

[49] Ibid.

[50] Ibid.

[51] Ibid.

[52] Ibid.

[53] Ibid.

W. I. B. Beveridge, a medical historian, has identified five historical hallmarks of pandemic influenza: (1) sudden onset and duration of only a month or two, (2) rapid spread, (3) high morbidity and increased death rate, (4) impact on all populations, but particularly in the elderly and chronically ill, and (5) an acute illness.[54] These criteria have assisted in identifying influenza pandemics prior to the isolation of the virus in 1933. Influenza's first global pandemic occurred in 1580, starting in Asia and infecting all of Europe in six weeks.[55] Rome reported some nine thousand deaths and some Spanish cities were nearly depopulated.[56] From the 1700s to the 1800s there were eight or nine potential pandemics.[57] I have chosen to focus on pandemic influenza starting in 1900 to highlight the public health impact of influenza even with the availability of modern vaccination and antiviral treatments. Four influenza pandemics have occurred since 1900: 1918, 1957, 1968, and 2009.

1918 Spanish Flu

The 1918 Spanish Flu has been called 'the greatest medical holocaust in history.[58] The devastation of the 1918 pandemic, even almost a century later, still strikes fear in the hearts of researchers, physicians, and the public. When a particularly severe influenza season is expected one of the first, and most persistent, questions is if there will be a repeat of the 1918 pandemic. The 1918 pandemic was the results of avian influenza

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[54] W. I. B. Beveridge, "The Chronical of Influenza Epidemics" *History and Philosophy of the Life Sciences* 13 no. 2 (1991):223-234.

[55] Beveridge, "The Chronical of Influenza Epidemics" 225.

[56] Beveridge, "The Chronical of Influenza Epidemics" 225.

[57] Ghendon, "Introduction to Pandemic Influenza through History" 451.

[58] Potter, "A History of Influenza" 575.

A H1N1 strain.[59] Despite its name, the Spanish Flu did not originate in Spain; rather the name was coined due to a particularly high incidence rate in Spain believed to be caused by the H1swN1 swine variant of the strain.[60] The virus spread worldwide in three waves: the first wave in US Army camps and civilian populations starting in January 1918 was mild.[61] This wave spread throughout Asia and Europe during the summer, disappearing from the US by late May 1918.[62] Switzerland had the first outbreak of the second wave in late July 1918, which spread worldwide by October with higher morbidity and mortality rates than the first wave.[63] Brevig Mission, an Eskimo outpost, is a haunting illustration of the devastation caused by the 1918 pandemic.[64] The first villagers reportedly perished on November 15, 1918; within five days, 90 percent of the village has died, "The Spanish Influenza did to Nome and the Seward Peninsula what the Black Death did to fourteenth century Europe."[65] The third wave spread worldwide between January and April 1919 causing a third of the pandemic deaths; the final wave is considered the most lethal due to its comparatively short duration.[66]

The 1918 Influenza Pandemic was the most efficient biological decimator of the human race.[67] The Plague of Justinian (bubonic plague) took 50 years to kill 100 million people. Smallpox and measles reduced the world's population by 90 million over four

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[59] Carlos Franco-Paredes, et. al., "H1N1 Influenza Pandemics: Comparing the Events of 2009 in Mexico with Those of 1976 and 1918-1919," *Archives of Medical Research* 40 (November 2009): 669-72, 671.

[60] Ghendon, "Introduction to Pandemic Influenza through History," 451.

[61] John M. Barry, "Observations on Past Influenza Pandemics," *Disaster Medicine and Public Health Preparedness* 3, Suppl. 2 (December 2009): S95-S99.

[62] Barry, "Observations on Past Influenza Pandemics," S95.

[63] Ibid., S95.

[64] Madeline Drexler, Emerging Epidemics: The Menace of New Infections, New York, New York: Penguin Books, 2009, 160.

[65] Ibid.

[66] Barry, "Observations on Past Influenza Pandemics," S95.

[67] Drexler, Emerging Epidemics, 163.

centuries.[68] The 1918 influenza took the majority of its 103 million lives in just four months.[69] In the United States alone the 1918 pandemic claimed 550,000 lives- ten times the number of people killed in World War I.[70] It is estimated that up to 80 percent of the US Army deaths in World War I involved influenza infection.[71] It is estimated that 50 percent of the world's population was infected during the 1918 pandemic.[72] A defining characteristic of the 1918 pandemic is the excess death among young adults between twenty and forty years of age, known as a W-shaped mortality pattern, instead of the excess mortality in infants and the elderly as seen in seasonal influenza.[73] The 1918 influenza strain launched a blitzkrieg attack on the human immune system, "People descended from apparently robust health to death's door in an hour."[74] Pregnant women not only suffered miscarriages but 41 percent of those who miscarried later died of influenza.[75] The majority of the 1918 influenza deaths did not occur from secondary bacterial pneumonia infections but from hemorrhaging due to the virus itself, described by a New York physician as, "They're blue as huckleberries and spitting blood."[76]

The 1918 pandemic demonstrated the social and economic impact of influenza pandemics. During peak infection times, worker shortages adversely impacted

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[68] Ibid.

[69] Ibid. There are conflicting reports on the number of deaths from 1918 influenza; some as low as 40 million others as high as 150 million.

[70] Ghendon, "Introduction to Pandemic Influenza through History" 451.

[71] Robert G. Webster, "Influenza: An Emerging Microbial Pathogen," Chap. 9 In Emerging Infections edited by Richard M. Krause. *Biomedical Research Reports* 275-300, 276. Cambridge Massachusetts: Elsevier 1998.

[72] C. W. Potter, "A History of Influenza," *Journal of Applied Microbiology* 91, no. 4 (October 2001): 572-79, 576.

[73] Yu-Chia Hsieh, et al., "Influenza Pandemics: Past, Present and Future," *Journal of the Formosan Medical Association* 105, no. 1 (January 2006): 1-6, 3.

[74] Drexler. Emerging Epidemics, 162.

[75] Ibid.

[76] Ibid.

government services with at least 25 percent of public servants failing to report for duty.[77] Hospitals and morgues were full and garbage piled in the streets. Mass graves had to be used in Alaska:

> Using steam generators, the miners melted a long rectangular gash in the Earth. The victims were each tied with a rope around the chest, dragged across the ice, and laid side by side at an Army regulation depth of six feet. Two tall wooden crosses, visible atop the bluff from the sea, marked the grave.[78]

Cities implemented social distancing measures, closing schools, churches, and theaters to prevent spreading infection, reminiscent of the measures that were taken during the Black Death.[79] Given the massive economic, social, and human impacts of the 1918 Spanish Flu, it is not surprising that a repeat performance is the greatest fear during particularly harsh influenza seasons and pandemics. The 1918 pandemic occurred prior to the identification of the influenza virus, had a vaccine been available, the impact of the pandemic may have been very different.

1957 Asian Influenza

Influenza A, H2N2 caused the pandemic of 1957.[80] The virus strain was isolated in the Yunan Province of China in 1957 and with high rates of infection in China in March, reaching Hong Kong in April.[81] The virus next spread throughout Asian in00to

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[77] Monica Schoch-Spana, "'Hospital's Full-Up': The 1918 Influenza Pandemic," *Public Health Reports* 116, Suppl. 2 (2001): 32-33, 32.

[78] Drexler, Emerging Epidemics, 160-161

[79] Stephen S. Morse, "Pandemic Influenza: Studying the lessons of history," Proceedings of the National Academies of Science 104 no. 18 (May 1, 2007): 7313-7314, 7313.

[80] J. K. Taubenberger, and D.M. Morens, "Pandemic Influenza- including a risk assessment of H5N1," *Revue scientifique et technique* 28 no. 1 (2009):187-202.

[81] Potter, "A History of Influenza," 577.

Singapore, Taiwan, and Japan.[82] The global spread of the infection was assisted by a large conference in Grinnel, Iowa with 1800 attendees from forty-three states and countries, including the Asian epidemic area. An outbreak of 200 cases occurred during the conference and allowed the virus to spread as individuals returned home.[83] Within six months of the conference, the virus had spread worldwide, leading to approximately 80,000 deaths in the United States.[84]

The 1957 pandemic was the first time the global spread of influenza could be studied in real time via laboratory investigations. This pandemic allowed researchers to understand the involvement of pneumonia in influenza infections and death.[85] Deaths due to viral pneumonia, described as patients "literally drown in their own bloody secretions," which also occurred during 1918 pandemic, were determined to be rare.[86] Simultaneous infection with viral and bacterial pneumonia was also seen during the 1957 pandemic. Sequential infection of influenza followed by bacterial pneumonia was determined to be the most common.[87] This increased understanding allows for better treatment and surveillance for complications. While the fatality rate was not particularly high (especially in comparison to the 1918 pandemic) 40,000 deaths were attributed to the infection in the United States. The 1957 pandemic illustrates that the disease need not be particularly fatal to warrant designation as a pandemic.[88] The virus became seasonally

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[82] Ibid.
[83] Ibid.
[84] Ibid.
[85] Burke A. Cunha, "Influenza: Historical Aspects of Epidemics and Pandemics." *Infectious Disease Clinics of North America*, 18 (2004): 141-155, 145. doi:10.1016/S0891-5520(03)00095-3.
[86] Ibid., 146.
[87] Ibid.
[88] Beveridge, 229.

endemic worldwide within two years and eventually disappeared from circulation within eleven years.[89]

1968 The Hong Kong Flu

The virus that caused the 1968 pandemic was first isolated in Hong Kong as an Influenza A H3N2 strain.[90] In the United States mortality was estimated at 34,000 compared to the then normal 20,000 seasonal deaths.[91] There was mild morality during the virus's first circulation with some locations reporting fewer deaths than in non-pandemic years.[92] Elderly patients experienced lower than usual infection rates with the Hong Kong Flu, potentially due to acquired immunity from prior infections.[93] The virus recurred the following winter, resulting in a reported 30,000 deaths in the United Kingdom during an eight-week period, potentially a second pandemic wave.[94] This strain has circulated globally since.[95]

2009 H1N1 Swine Flu

In the age of international, high-speed travel an influenza pandemic is all but inevitable. Influenza researcher Robert Webster remarked, "We have all been preparing for a pandemic, H1N1 [Avian Influenza], has been at the top of our list and surprise,

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[89] J. K. Taubenberger, and D.M. Morens, "Pandemic Influenza- including a risk assessment of H5N1"

[90] Hsieh, et al., "Influenza Pandemics: Past, Present, and Future," 2.

[91] John M. Barry, "Observations on Past Influenza Pandemics," *Disaster Medicine and Public Health Preparedness* 3, Suppl. 2 (December 2009): S95-S99, S97.

[92] J. K. Taubenberger, and D.M. Morens, "Pandemic Influenza- including a risk assessment of H5N1."

[93] Brasseur, 26.

[94] Beveridge, 229.

[95] J. K. Taubenberger, and D.M. Morens, "Pandemic Influenza- including a risk assessment of H5N1."

surprise, 2009 H1N1 influenza A came out of left field."[96] The 2009 H1N1 Swine Flu pandemic created global panic, proved how quickly influenza could spread worldwide and reinforced the importance of sharing information internationally.

On March 18, 2009, Mexico City reported a case of influenza-like illness, which was later confirmed to be influenza A H1N1.[97] A month later, April 17th, the CDC confirmed two California children were infected with the same influenza A strain H1N1 that was previously confirmed in Mexico.[98] The influenza strain was determined to be resistant to amantadine and rimantadine (Flumadine) with eventual sporadic reports of oseltamivir (Tamiflu) resistance.[99] The influenza virus responsible for these infections was a triple reassortment virus closely related to North American and Eurasian swine-origin influenza viruses that had not been previously identified in humans or other animals.[100] Unlike previously reported H1N1 infections, where the patient had direct contact or proximity to pigs, neither child had livestock contact- indicating a new human virus.[101] The CDC uploaded the complete gene sequence to a publicly accessible influenza database to allow scientists from around the world to use the information and contribute their findings.[102]

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[96] Institute of Medicine, Institute of Medicine (US) Forum on Microbial Threats. *The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic: Global Challenges, Global Solutions: Workshop Summary.* Washington, D.C.: National Academies Press, 2010.

[97] R. A. Stein, "Lessons from Outbreaks of H1n1 Influenza," *Annals of Internal Medicine* 151, no. 1 (July 7 2009): 59-62, 59. Influenza-like-illness is diagnosed when a patient has the symptoms of influenza but a culture is not taken, is negative or inconclusive.

[98] Stein, "Lessons from Outbreaks of H1N1 Influenza" 59.

[99] Institute of Medicine. Institute of Medicine (US) Forum on Microbial Threats.

[100] Centers for Disease Control and Prevention, The 2009 H1N1 Pandemic: Summary Highlights, April 2009-April 2010, Last Modified June 16, 2010, http://www.cdc.gov/h1n1flu/cdcresponse.htm; A triple reassortment virus is one that has passed between three species; in this case birds, pigs and humans.

[101] Centers for Disease Control and Prevention, The 2009 H1N1 Pandemic: Summary Highlights.

[102] Centers for Disease Control and Prevention, The 2009 H1N1 Pandemic: Summary Highlights.

On April 23, 2009, Mexico reported a rising epidemic of the same strain.[103] By May 13, 2009, H1N1 was reported in twenty-eight countries.[104] Margaret Chan, the WHO's Director-General decided on May 21, 2009, that H1N1 would not be declared a pandemic "not because of any epidemiological rationale but because the very term 'pandemic' was feared to trigger a global panic."[105] Director-General Chan understood the requirement to balance the epidemiological evidence with the needs of society; while the H1N1 virus was widespread, it was not particularly lethal. Of interesting note, since 1918 pandemics have been successively less lethal. This may be the result of available vaccination or evolution of the virus; the reasoning is unknown. Nonetheless, the lower lethality does not make the virus less burdensome. While Director Chan did not specifically cite this as rational for not wanting to declare H1N1 a pandemic the lack of lethality may have played a role. While people were ill and dying, Director Chan may have been sensitive to the issue of threat fatigue, because while H1N1 reached pandemic levels, it was not as lethal as it could have been, sounding the alarm risked future noncompliance. Despite the initial refusal, the World Health Organization declared H1N1 to be a pandemic on June 11, 2009.[106] The declaration of a pandemic by the WHO signified that, although the majority of reported cases were clinically moderate, H1N1 was a worldwide threat. The designation was important because as a pandemic, H1N1 was able to be treated by governments as a public health emergency allowing for

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[103] Carlos Del Rio, and Mauricio Hernandez-Avila, "Lessons from Previous Influenza Pandemics and from the Mexican Response to the Current Influenza Pandemic," *Archives of Medical Research* 40, no. 8 (November 2009): 677-80, 678.

[104] Stein, "Lessons from Outbreaks of H1N1 Influenza," 59.

[105] Sander Gilman, "The art of medicine moral panic and pandemics," *Lancet* 375 (May 29, 2010): 1866-1867, 1866.

[106] Del Rio and Hernandez-Avila, "Lessons from Previous Influenza Pandemics," 678.

specialized regulations to be used to control infection Of seventy-seven confirmed H1N1 United States deaths reported by the CDC the median age was thirty-eight (range two months to eighty-four years) with underlying conditions of "morbid obesity, hypertension, cardiovascular disease, pregnancy, and asthma" being present in 90 percent of cases.[107] The elderly did not experience as high rates of infection with H1N1 as historically experienced with seasonal influenza; although the remaining groups represent target populations.[108] Primary viral pneumonia was a major contributor to death along with bacterial co-infections.[109] Pulmonary embolism was detected in approximately 15 percent of cases.[110] Pneumonia, embolism, and bacterial infections are some of the severe outcomes the influenza vaccine seeks to prevent.

Vaccination is the best defense against influenza infection. As a novel virus, no vaccine against H1N1 was available immediately to aid the pandemic control effort. In order to start the vaccine development process, CDC began developing its candidate virus strain a day after the second patient's virus strain was identified.[111] According to CDC Influenza Division Director Nancy Cox, the decision to move forward so quickly with the development of the vaccine candidate was made because "there was absolutely no evidence that the first two patients had any contact with livestock, and we had also heard that there was influenza-like illness activity in contacts of the two individuals, so we

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[107] Institute of Medicine. Institute of Medicine (US) Forum on Microbial Threats.

[108] National Center for Immunization and Respiratory Diseases, CDC. "Use of Influenza A (H1N1) 2009 Monovalent Vaccine," Morbidity and Mortality Weekly 58, no. (Early Release) (August 21, 2009): 1–8. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr58e0821a1.htm.

[109] Institute of Medicine. Institute of Medicine (US) Forum on Microbial Threats.

[110] Ibid.

[111] Ibid. Candidate virus strains are the virus strains that have been processed specifically to be used in vaccine production.

thought it was better to be safe than sorry."[112] On July 22, 2009, the NIH announced that clinical trials were ready to begin for the H1N1 vaccine.[113] The following day, the FDA's Vaccine and Biological Advisory Committee publicly supported the proposed plan to license the 2009 monovalent vaccine under the strain change pathway allowing the H1N1 vaccine to use the same licensing approval process as the seasonal vaccine and thus be available to the public faster.[114] This was the key to the success of any vaccination program because FDA approval is required prior to distribution of any new drug. An Investigational New Drug application is a time and resource intensive process requiring millions of dollars and years of work, which is not feasible for seasonal or pandemic influenza vaccines. Initial supplies of the vaccine were limited due to manufacturing capabilities thus a distribution scheme needed to be developed.

The Advisory Committee for Immunization Practices (ACIP), the immunization advisory board of the CDC, met on July 29, 2009, to make target-population recommendation for the H1N1 vaccine. The ACIP reviewed available epidemiologic and virology data that indicated groups at higher risk for infection and severe complications to determine who should receive the vaccine.[115] The ACIP recommended the following populations receive initial priority: pregnant women, people who live with or care for infants under six months of age, healthcare, and emergency medical services workers, children and young adults ages six months to twenty-four years of age, and adults twenty-

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[112] Ibid.
[113] Centers for Disease Control and Prevention, The 2009 H1N1 Pandemic: Summary Highlights.
[114] Ibid.
[115] Ibid.

four to sixty-two with chronic health disorders.[116] Senior citizens were not amoung the target-populations for the H1N1 pandemic vaccine. This was a significant departure from prior recommendations as the elderly have always been considered a priority. The elderly were not included in the target-populations because they had lower rates of infection.[117] The ACIP also gave local public health authorities and healthcare professionals the authority to expand programs as the need and availability of vaccine changed in their areas.[118]

Development of the H1N1 vaccine was completed in August 2009. The CDC expanded its license with McKesson Specialty Distribution to provide centralized distribution of the vaccine, which was allotted to each state based on population.[119] States were responsible for placing their orders although administering providers were asked to sign a Provider Agreement assuring that they intended to adhere to the target-population recommendations and their state's requirements.[120] On September 30, 2009, states began submitting orders with the first doses being administered on October 5, 2009.[121] Although initial supply was restricted and greatly outpaced demand, by late November/early December 2009, most states allowed the vaccine to be administered to all populations with 74 percent of the vaccine given to those in the initial priority/target groups.[122] By April 2010, the pandemic strain of H1N1 had caused approximately 60.8 million

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[116] Ibid.

[117] National Center for Immunization and Respiratory Diseases, CDC. "Use of Influenza A (H1N1) 2009 Monovalent Vaccine," *Morbidity and Mortality Weekly* 58, no. (Early Release) (August 21, 2009): 1–8. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr58e0821a1.htm.

[118] Centers for Disease Control and Prevention, The 2009 H1N1 Pandemic: Summary Highlights.

[119] Ibid.

[120] Ibid.

[121] Ibid.

[122] Ibid.

infections, 274,304 hospitalizations and 12,469 deaths in the United States.[123] The pandemic strain has circulated worldwide since 2009.

1976 Pandemic Panic

The events of 1976, although not a pandemic, warrant discussion to illustrate the challenges faced by researchers and policy makers. Several soldiers at Fort Dix died in early 1976 of a swine flu virus thought to be a direct descendant of the 1918 influenza virus.[124] The comparisons to the 1918 pandemic started from the beginning as the 1918 pandemic started in Army camps as well. The general sense of alarm was tempered when it was noted that influenza pandemics tended to start as a cloudburst of cases, and this had not occurred.[125] The Public Health Service launched a program to immunize 50 million people against influenza due to the fear that this virus strain could result in a repeat of the 1918 Spanish Flu.[126] The rationale behind the response was that "[t]he administration can tolerate unnecessary health expenditures better than unnecessary death and illness, particularly if a flu pandemic should occur."[127] The response was known as the "National Influenza Immunization Program" or the Swine Flu Program.[128] The program was a logistical success:

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[123] Sundar S, Shrestha, et al., "Estimating the Burden of 2009 Pandemic Influenza A (H1N1) in the United States (April 2009-April 2010)," *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 52 Suppl 1 (January 1, 2011): S75–82. doi:10.1093/cid/ciq012.

[124] Richard Krause, "The Swine Flu Episode and the Fog of Epidemics," *Emerging Infectious Diseases* 12, no. 1 (January 2006): 40-43, 41.

[125] Ibid.

[126] Ibid.

[127] Sander Gilman, "The art of medicine moral panic and pandemics" *Lancet* 375 (May 29, 2010): 1866-1867, 1866.

[128] George Dehner, "WHO Knows Best? National and International Response to the Pandemic Threats and the 'Lessons' of 1976." *Journal of the History of Medicine and Allied Sciences* 65 no. 4 (October 2010): 478-513, 479.

> We proved it was possible to organize a mass influenza immunization program from start to finish: identify the virus, grow up stocks, prepare and field test the vaccine, provide for indemnity, and immunize a large segment of the population, all within 10 months.[129]

The logistical success of the program is impressive; in comparison, the 2009 H1N1 vaccine took eight months to be widely available despite having almost thirty years to improve technology, but the Swine Flu program was still labeled a fiasco. The *New York Times* declared the program a political ploy to increase the CDC's budget and a "panicky overreaction to a minimal threat."[130] Despite the impressive preparation, the pandemic never occurred, and the vaccine was blamed for an increase in Guillain-Barre syndrome occurrence in vaccine recipients and tied to several deaths.[131] Janet Kinney received the 1976 swine flu vaccine and was one of the approximately 500 people that developed Guillain-Barre, a rare neurological condition that causes temporary muscle weakness and paralysis.[132] A week after receiving the vaccine, Ms, Kinney was "so weak I couldn't push down the toaster button." Instead of being protected against a pandemic virus, she spent a month in the hospital paralyzed from the neck down. Why the 1976 influenza vaccine was associated with Guillian-Barre is a mystery as no other influenza vaccines have been linked to the condition. Ms. Kinney is one of many people who are unwilling to receive influenza vaccines because of the 1976 swine flu program.[133] Although the cause of Guillain-Barre cases may never be known, the influenza vaccine

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[129] Krause, "The Swine Flu Episode and the Fog of Epidemics" 42.

[130] Harry Schwartz, "Swine Flu Fiasco" *The New York Times*. December 21, 1976, 33.; Harry Schwartz, "Soft Evidence and Hard Sell," *The New York Times.* September 5, 1976, 137.

[131] Dehner, "WHO Knows Best?" 480.

[132] Andrew Pollack, "Swine Flu Fears of 1976 Offer Lessons, and Concerns," *The New York Times*, May 8, 2009. http://www.nytimes.com/2009/05/09/health/09vaccine.html?_r=0.

[133] Ibid.

will always be linked to the Guillain-Barre in the public's memory, regardless of the number of studies that show the vaccine is safe. Dr. David Spencer, the CDC Director during the National Swine Flu Program, commented in 2009 that "People have to make science the priority. They have to rely on science rather than politics."[134]

Pandemics create a particular challenge for influenza vaccine programs due to their unpredictable nature and the methods used for influenza vaccine production. Pandemic influenza differs from seasonal influenza with higher death rates in younger populations, successive pandemic waves, and higher rates of transmission.[135] As previously discussed, pandemics are caused by antigenic shift; meaning that there is no vaccine in current production. During the 2009 H1N1 pandemic, a vaccine was available within six months of the virus being detected, but the vaccine was not widely available until after the highest rate of infection (October to November 2009) had passed.[136] Vaccine manufacturing takes at least six months due to the use of the egg-based method which will be discussed in the following section. Influenza vaccination policies must be flexible enough to accommodate changes in target-populations during pandemics while also providing clear guidance during interpandemic periods.

The H1N1 Pandemic provided an example of how successful influenza vaccine policy can work. The ACIP met to determine target-population recommendations for the pandemic vaccines based upon prevailing epidemiological evidence regarding infection

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[134] Shari Roan, "Swine Flu 'Debacle' of 1976 Is Recalled - Latimes." *The LA Times*, April 27, 2009. http://articles.latimes.com/2009/apr/27/science/sci-swine-history27.

[135] M. A. Miller, C. Viboud, M. Balinska, and L. Simonsen, "The Signature Features of Influenza Pandemics--Implications for Policy," *New England Journal of Medicine* 360, no. 25 (June 18, 2009): 2595-8, 2595.

[136] S. C. Redd, T. R. Frieden, A. Schuchat, and P. A. Briss, "1918 and 2009: A Tale of Two Pandemics," *Public Health Reports* 125 Suppl 3 (April 2010): 3-5.

and hospitalization rates. This allowed the CDC to work alongside the states to ensure that the right populations received the vaccine at the right time. Future influenza vaccine policy, especially during a pandemic, must also be based on high quality, up-to- date epidemiological and clinical evidence.

VACCINE BACKGROUND

The goal of influenza vaccination is to prevent severe disease and death in the high-risk populations while also decreasing the overall rate of illness and burden of disease throughout the population.[137] Influenza vaccines work by eliciting a strain-specific immune response and are recommended annually.[138] Smorodinsteff, a researcher in the then USSR, created the first influenza vaccine in 1936.[139] It was a live-attenuated vaccine with questionable efficacy and safety results.[140] Development of the inactivated influenza vaccine began in 1937 with Francis Magill, in the United States, and Andrewes and Smith (the same researchers who originally isolated the virus), in England, using animal models.[141] The first human trials of inactivated influenza vaccine were completed during World War II using the US military as subjects with the first commercial vaccine becoming available in 1945.[142] W.M. Stanley's 1944 publication

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[137] World Health Organization, "Adoption of Global Agenda on Influenza-part II." *Weekly Epidemiological Record* 77, no. 23 (June 7, 2002): 191-196.

[138] World Health Organization, "Influenza Vaccines WHO Position Paper" *Weekly Epidemiological Record* 80, no. 33 (August 19, 2005): 277-88.

[139] Kristen Kuszewski and Lidia Brydak. "The Epidemiology and History of Influenza" *Biomedicine & Pharmacotherapy* 54, no. 4 (May 2000): 188-95, 188.

[140] Ibid. Efficacy and safety were based upon self-report.

[141] John Oxford, Robert Lambkin-Williams, and Anthony Gilbert. "Influenza vaccines have a short but illustrious history." In *Influenza Vaccines for the Future* edited by R. Rappuoli and G. Del Giudice, 31-64. Basal Switzerland Birkhauser: 2008.

[142] Richard John Webby, and Matthew Robert Sandbulte, "Influenza Vaccines" *Frontiers in Bioscience* (May 1, 2008): 4912-4924, 4914.

detailed the preparation and procedures used to create the influenza vaccine for commercial use.[143] This publication acted as a protocol for the commercial manufacturing process which has been used, with safety and efficiency improvements, since its publication. The influenza vaccine manufacturing process has four steps. First, the vaccine virus is injected into eggs.[144] After two to three days of incubation, the virus is then harvested from the allantoic fluid (or egg white).[145] Then the virus is killed with formalin, purified, and tested.[146] Finally, the vaccine is diluted and packaged for shipping. These steps are dependent on other processes, including the identification of the seasonal virus strains, the preparation of the vaccine virus strains (known as the candidate virus strains) and, most importantly, the availability of the eggs.

Types of Vaccine

There are two main types of influenza vaccine that have been used in the United States: inactivated and live attenuated. Additional types including recombinant and cell-culture have also become available in recent years.

Inactivated vaccine production uses a similar process to the one first used in the 1940s. The virus is grown in chicken eggs, then concentrated and chemically inactivated.[147] The vaccine is formulated to 15-µg hemagglutinin proteins per virus strain per dose, meaning a trivalent vaccine would have 45-µg of hemagglutinin. The hemagglutinin protein is used in the vaccine because it is the protein that attaches to the

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[143] Hannoun, “The evolving history of influenza viruses and influenza vaccines."

[144] Catherine Gerdil, "The annual production cycle for influenza vaccine," *Vaccine* 21(2003):1776-1779, 1777.

[145] Ibid.

[146] Ibid.

[147] Webby, "Influenza Vaccines,” 4914.

host cell; antibodies that bind to the hemagglutinin prevent attachment and thus infection.[148] Inactivated vaccines are administered via injection.

Live attenuated vaccines were approved for influenza use in the United States since 2003.[149] Unlike inactivated vaccines, live attenuated vaccines stimulate humoral and cellular immune responses by replicating in the upper respiratory tract.[150] In live attenuated vaccine (LAV) production, the hemagglutinin and neuraminidase of the candidate strains are inserted into the master, cold-adapted strain (based on A/Ann Arbor/6/60 and B/Ann Arbor/1/66) and then replicated in eggs.[151] In the United States, LAV was approved for healthy, non-pregnant people ages two through forty-nine and is administered intranasally. The intranasal route gave a vaccination option to those patients who are particularly needle adverse, making it ideal for children. However, as of 2016 the live attenuated influenza vaccine is no longer recommended as it was determined to be ineffective.[152] Long-term efficacy studies showed that the LAV vaccine was not effective in preventing influenza infection. For the 2015-2016 influenza season, the LAV vaccine only had a 3 percent efficacy rate against the circulating strains which followed low results for the previous two seasons.[153]

Inactivated and live attenuated vaccines both have drawbacks. The minimum six - to seven-month production timeline for either type of vaccine, is the first and perhaps

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[148] Ibid.

[149] Ji Yun Noh, and Woo Joo Kim, "Influenza Vaccines: Unmet Needs and Recent Developments," *Infection & Chemotherapy* 45, no. 4 (December 2013):375-386, 378.

[150] Richard John Webby, and Matthew Robert Sandbulte, "Influenza Vaccines," F*rontiers in Bioscience* (May 1, 2008): 4912-4924, 4914.

[151] Webby, "Influenza Vaccines," 4914.; Ellebedy, "Influenza Vaccines" D66.

[152] Susan Scutti. "CDC Panel Recommends against Using FluMist Vaccine - CNN.com." CNN Health, June 22, 2016. http://www.cnn.com/2016/06/22/health/cdc-flumist-nasal-spray-flu-vaccine/.

[153] Centers for Disease Control and Prevention. "ACIP Votes Down Use of LAIV for 2016-2017 flu season." Media Release. June 22, 2016. https://www.cdc.gov/media/releases/2016/s0622-laiv-flu.html

most significant drawback. Second, is the dependence on eggs for manufacturing. The egg requirement creates a potential supply chain problem but also a contradiction for anyone allergic to eggs. Finally, both inactivated and live-attenuated vaccines require two doses for naïve children. Developments in vaccine manufacturing including adjuvants and new manufacturing processes attempt to address these issues.

Adjuvanted vaccines are inactivated vaccines with additives to enhance the immune response. Mineral oil was used in the 1950s but had severe local side effects.[154] Currently, MF59 is the licensed adjuvanted influenza vaccine in the US. MF59 is an oil-in-water emulsion that was first approved in Europe in 1997 and has shown to increase the effectiveness of inactivated vaccines in the elderly.[155]

Cell-culture vaccines overcome the potential supply problems and contradictions created by egg use while decreasing the manufacturing timeline.[156] Cell-culture manufacturing was approved for influenza vaccines in 2012.[157] In cell-culture manufacturing, candidate strains are grown in dog kidney cells then purified and formulated in the same manner as inactivated vaccines.[158]

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[154] Noh and Kim, “Influenza Vaccines: Unmet Needs and Recent Developments” 379.

[155] Ibid.

[156] Centers for Disease Control and Prevention. How Influenza (Flu) Vaccines are Made. Last Updated January 6, 2015. Accessed January 26, 2016. http://www.cdc.gov/flu/protect/vaccine/how-fluvaccine-made.htm

[157] Food and Drug Administration, "The Evolution, and Revolution, of Influenza Vaccines." FDA Consumer Health Information. January 18, 2013.

[158] Ernest Milian, and Amine A. Kamen, "Current and Emerging Cell Culture Manufacturing Technologies for Influenza Vaccines," *BioMedical Research International* Volume 2015, Article ID 504831.

Recombinant vaccines were approved for influenza in 2013.[159] Recombinant vaccines reduce manufacturing timelines and are safe for patients with allergies to eggs.[160] The shorter timeline is valuable not only during pandemic responses but also when a new influenza virus strain is circulating that was unexpected eight months prior. Manufacturers use recombinant hemagglutinin protein and produce the vaccine in insect cells.[161] Once the vaccine is prepared, it is then purified as 45µg per virus strain per dose and sent to testing.[162]

The United States currently offers influenza vaccines in quadrivalent (protection against four virus strains) and trivalent (protection against three virus strains) formulations in both low- (9µg per virus strain when given by the intradermal route) standard- (15µg per virus strain when given by the subcutaneous or intramuscular routes) and high-dose (60µg per virus strain by intramuscular for senior citizens) formulations.[163] Four different manufacturers offer eleven influenza vaccines.[164]

Influenza Vaccine Production

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[159] Food and Drug Administration, "The Evolution, and Revolution, of Influenza Vaccines." FDA Consumer Health Information. January 18, 2013.

[160] Katherine Houser and Kanta Subbarao. “Influenza Vaccines: Challenges and Solutions,” *Cell Host & Microbe* 17, no. 3 (March 11, 2015): 295–300. doi:10.1016/j.chom.2015.02.012.

[161] Centers for Disease Control and Prevention, “How Influenza (Flu) Vaccines are Made” Last Updated January 6, 2015. Accessed January 26, 2016. http://www.cdc.gov/flu/protect/vaccine/how-fluvaccine-made.htm

[162] Katherine Houser and Kanta Subbarao. “Influenza Vaccines: Challenges and Solutions,” *Cell Host & Microbe* 17, no. 3 (March 11, 2015): 295–300. doi:10.1016/j.chom.2015.02.012.

[163] Lisa A. Groshskopf, Leslie Z. Sokolow, Sonja Olsen, Joseph S. Breese, Karen R. Broder, and Ruth A. Karron, "Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2015-16 Influenza Season." *Morbidity and Mortality Weekly Report* 64, no. 30 (August 7, 2015): 818-825.

[164] Ibid. The complete list of US influenza vaccines and manufactures is located in the appendix of this chapter

The vaccine production timeline is deceptively straightforward. The WHO selects the northern hemisphere's strains in February.[165] Production occurs from March to June with regulatory approval following in July to September.[166] Vaccines are then available in mid-to-late September or early October.[167] For the southern hemisphere, strains are selected in September with production until mid-January.[168] Regulatory approval takes until mid-March with the vaccines available by early April. In reality, the yearly influenza production schedule is much more complex.

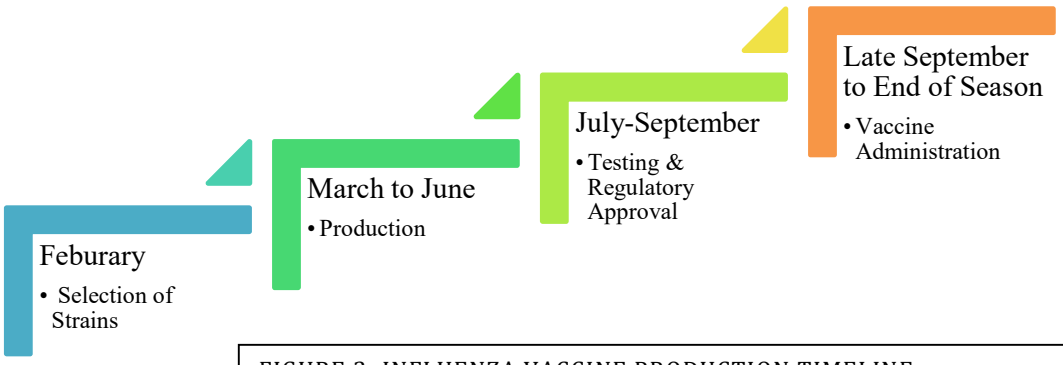

FIGURE 2: INFLUENZA VACCINE PRODUCTION TIMELINE

The yearly influenza vaccine is dependent upon worldwide surveillance data to provide an accurate prediction of the included strains. Influenza surveillance has been a priority of the World Health Organization since its establishment in 1948. In July 1947, a group of experts recommended the establishment of international influenza coordinating center to collect and distribute information. The National Institute for Medical Research in London became the first World Influenza Center, commencing the WHO Influenza Program, with the objective to "assist in plans against the possible recurrence of a

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[165] Philip Lambach, et al., "Consideration of strategies to provide influenza vaccine year round," Vaccine 33 (August 2014): 6493-6498, 6495.
[166] Ibid., 6495.
[167] Ibid.
[168] Ibid.

pandemic, and in devising control methods to limit the spread, severity, and consequences of the disease."[169] National laboratories with the capacity to isolate the influenza virus who were willing to share their findings were recruited to assist with the effort. Within four years the program expanded to include sixty laboratories in forty countries and the Strain Study Center for the Americas was established in New York.[170] Today, the Global Influenza Surveillance and Response System (GISRS) includes six WHO Collaborating Centers, four WHO Essential Regulatory Laboratories, and thirteen WHO reference laboratories.[171] Through these centers and laboratories the WHO coordinates worldwide surveillance to determine the circulating influenza strains.[172] The WHO, through the Strategic Advisory Group of Experts on immunization (SAGE), makes biannual (February and October) recommendations regarding the strains of influenza to be included in the vaccine.[173]

Influenza vaccine production is often not a smooth process. The WHO Collaborating Centers prepare high-growth seed strains to be used in vaccine production.[174] Vaccine manufacturers then test the strains and begin production. Production must be carefully planned due to dependence on eggs, the need for two production cycles, and the requirement for the vaccine to be available prior to the influenza season. Production bottlenecks occur due to the reagents becoming available

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[169] World Health Organization, "WHO influenza surveillance," *Weekly Epidemiological Record* 71 no. 47 (November 22, 1996) 353-354, 353.

[170] Ibid.

[171] World Health Organization, Global Influenza Surveillance and Response System (GISRS). Accessed January 16, 2016. http://www.who.int/influenza/gisrs_laboratory/en/

[172] Catherine Gerdil, "The annual production cycle for influenza vaccine," *Vaccine* 21(2003):1776-1779, 1777.

[173] Ibid.

[174] Ibid. High-growth seed strains are essential virus concentrate used to grow the vaccine in the embryonated eggs.

approximately three months after the strain selection.[175] The reagents are required to test the potency of the vaccine. This bottleneck exists because only four laboratories supply the reagents for the entire world: Therapeutic Goods Administration (Australia), National Institute for Infectious Disease (Japan), National Institute for Biological Standards and Control (United Kingdom) and the Center for Biologic Evaluation and Research (United States).[176]

The 2004/2005 influenza season illustrated the frailty of the influenza vaccine production process. A worldwide influenza vaccine shortage occurred after a British manufacturer was forced to halt production due to contamination.[177] Vaccine redistribution required time and resource commitments; lack of synchrony and communication between supply and demand created surpluses in some areas less than ninety days after the shortage began.[178] The United States is in a particularly vulnerable position due to its dependence on foreign manufacturers; "[w]e need a surge capacity,' said Julie Gerberding, director of the Centers for Disease Control and Prevention in Atlanta, Georgia, and 'we simply do not have it.'"[179] The lack of surge capacity is one of the reasons target-population recommendations exist. In the event of a shortage, which

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[175] Ibid. A reagent is a compound used to test the strength of the influenza vaccine. Can also be used to test for the presence of another compound via the chemical reaction.

[176] Ernest Milian, and Amine A. Kamen, "Current and Emerging Cell Culture Manufacturing Technologies for Influenza Vaccines," *BioMedical Research International* Volume 2015, Article ID 504831.

[177] Helen Pearson, "US Lacks Back-up for Flu Vaccine Shortfall," *Nature* 431, no. 7010 (14 October 2004): 726.

[178] Monica Schoch-Spana, Joseph Fitzgerald, Bradley R. Kramer, and the UPMC Influenza Task Force, "Influenza Vaccine Scarcity 2004-05: Implications for Biosecurity and Public Health Preparedness," *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science* 3, no. 3 (2005): 224-334.

[179] Pearson, "US Lacks Back-up for Flu Vaccine Shortfall," 726.

can occur for a multitude of reasons, people at high risk of severe outcomes and death receive priority access to available supplies.

Conclusion

The influenza virus is able to thwart attempts at control due to its ability to consistently and unpredictably evolve. Since the first influenza global pandemic in 1580, the influenza virus has proven to be a biological threat to humanity. While no pandemic has been more deadly than the 1918 Spanish Flu, the influenza virus causes severe socioeconomic and public health impacts each year. The influenza vaccine has reduced these impacts by protecting those at greatest risk of contracting the virus and suffering severe illness. Target-population recommendations allow the vaccine to be allocated to those with the highest need when supplies are short. Despite documents safety and efficacy of the influenza vaccine, vaccination rates are low, and the target-population recommendations have been criticized as being based on low-quality evidence. I aim to establish, throughout this project, that evidence-based influenza policy which is well communicated to the public will lead to better vaccination rates and thus lower public health burdens from influenza infections.

Chapter 2: Rhetoric and Policymaking

The influenza virus creates seasonal epidemics and unpredictable pandemics, as discussed in the previous chapters. Seasonal influenza epidemics can generally be prepared for with vaccination programs, but influenza pandemics are nearly impossible to prepare for due to the emergence of novel virus strains and the subsequent vaccine manufacturing timelines. Policy helps manage influenza outbreaks and reduces the yearly burden of influenza, strengthening of the health system infrastructure, and pandemic planning.[180] Target-population recommendations are one of the public health polices which manage and mitigate burdens from the influenza virus. Policy supports the reduction of the burden of influenza infections by requiring health insurers to provide coverage for the yearly vaccine which aids in preventing severe infections and helping control the spread of the virus. The target-population recommendations provide guidance on who should receive the vaccination, when the vaccine should be administered, and which formulation of the vaccine is most appropriate for each population. From the health system infrastructure standpoint, influenza policy helps strengthen community immunization programs via funding and information regarding vaccine availability and other public health services. The health system infrastructure is vital in pandemic planning by ensuring that there are sufficient locations for vaccine administration and people are informed as to where influenza vaccines are available. In order for policy to be successfully implemented, it must also be successfully communicated to the public. Target-population recommendations are easily accessible but inadequately communicated

[180] Target-population recommendations are not policy until they are accepted/adopted by an entity with legislative authority.

to the public. This chapter will discuss the process of policymaking and how classical rhetoric can be leveraged to facilitate the integration of high-quality clinical research to improve decision making and communication.

I advocate for the use of an evidence-based approach to policymaking.[181] The evidence-based approach to policymaking seeks to incorporate research into the policy-making process to "ensure that decision making is well-informed by the best available research evidence."[182] Within the realm of healthcare, evidence-based policy aims to increase the efficiency, effectiveness, quality, and appropriateness of healthcare services to improve overall population health status.[183] High-quality evidence allows policy makers to reduce error and bias by using a more systematic and transparent approach.[184] Basing influenza policy on the best research available is imperative to the creation of sound, ethical policy. I believe that incorporation and communication of well-designed, rigorously conducted research will address concerns of the influenza vaccine being ineffective, possibly harmful, the resulting illness caused by the virus inconsequential and the target-population recommendations being based on low-quality research.

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[181] The current processes used by the World Health Organization and the Centers for Disease Control and Prevention to create target-populations recommendations aim to be evidence-based. This chapter discusses the overarching processes of policymaking, the specific processed used for the target-population recommendations will be discussed next chapter.

[182] Andrew Oxman, John N. Lavis, Simon Lewin, and Atle Fretheim, "Support Tools for Evidence-Informed Health Policymaking (STP) 1: What Is Evidence-Informed Policymaking?" *Health Research Policy and System* 7 Suppl 1 (December 2009): S1.

[183] Harley D. Dickinson, "Evidence-Based Decision-Making: An Argumentative Approach," *International Journal of Medical Informatics* 51 (August 1998): 71-81, 71. doi:10.1016/S1386-5056(98)00105-1.

[184] Andrew Oxman, John N. Lavis, Simon Lewin, and Atle Fretheim, "Support Tools for Evidence-Informed Health Policymaking (STP) 1: What Is Evidence-Informed Policymaking?" *Health Research Policy and System* 7 Suppl 1 (December 2009): S1.

Successful implementation of an evidence-based policy approach avoids inconsequential research being simply inserted into policy to support claims.[185] Evidence-based policy involves a collaboration between researchers and policymakers. Research has the ability to improve and inform policymaking, although it is not an easy task. The most commonly cited barriers are mutual mistrust, lack of communication between researchers and policymakers, and the lack of relevant and available research.[186] These barriers must be overcome if evidence-based policymaking is to be successful. I contend that classical rhetoric can be leveraged to improve evidence-based policymaking for influenza vaccination by bridging the gap between policymakers, researchers, and the public. Improved communication between researchers and policymakers can lead to utilization of research to adapt and improve policy. Communication between researchers, policymakers, and the public allows for the concerns of the public to be addressed and has the potential to lead to higher compliance with the policy.

This chapter will be divided into three sections. The first will introduce the concept of classical rhetoric and the skill set of the rhetorician. The second will explore the process of policymaking including the challenges of evidence-based policymaking. The final section will provide an analysis of how the rhetorician's skill set can be leveraged to improve evidence-based policymaking.

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[185] Nick Black, "Evidence Based Policy: Proceed with Care," *BMJ* (Clinical Research Ed.) 323, no. 7307 (2001): 275–79. doi:10.1136/bmj.323.7307.275.

[186] Simon Innvaer, et al., "Health Policy-Makers Perceptions of Their Use of Evidence: A Systematic Review," *Journal of Health Services Research and Policy* 7, no. 4 (October 2002): 239–44. doi:10.1258/135581902320432778.

CLASSICAL RHETORIC

Classical rhetoric is the art of forming and articulating a logical, persuasive argument. In modern times, rhetoric has been tied to insincerity and arguments that lack meaningful content. I argue that the skills of the classical rhetorician are necessary to meet the challenges of evidence-based policymaking. The best rhetorical argument is able to address the intellectual and psychological concerns of the audience but "does not manipulate beliefs in order to make the worse appear to be the better course, but rather presents the best case in a way that is comprehensible and moving."[187] Communication of policy decisions is vital for compliance, especially in public health policy:

> The reality is that most measures for managing public health emergencies rely on public compliance for effectiveness. Measures ranging from hand washing to quarantine require public acceptance of their efficacy, as well as acceptance of the ethical rationale for cooperating with instructions that may limit individual liberty so as to protect the broader public from harm. This requires that the public trust not only the information they are receiving, but also the authorities who are the sources of this information, and their decision-making processes.[188]

It is not enough to simply tell everyone that the influenza virus is deadly, the vaccine is safe and should be administered at a particular time to specific groups. The communication of the target-populations and the rationale for those decisions must be accurate and compelling to build trust and encourage compliance. Communication of the target-population recommendations for the influenza vaccine requires the public to accept the recommendations as both accurate and fair. The recommendations must balance the

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[187] Amelie Okensberg Rorty, "The Directions of Aristotle's 'Rhetoric,'" *The Review of Metaphysics* 46, no. 1 (September 1992.): 63–95, 64.

[188] P. O'Malley, J. Rainford, A. Thompson, "Transparency during Public Health Emergencies: From Rhetoric to Reality," *Bulletin of the World Health Organization* 87 (2009): 614–18.

need for the target-populations to be vaccinated against influenza with preventing public panic, as well as encourage social distancing measures. Successful communication will encourage the target-populations to be vaccinated immediately, promote the implementation of the recommended social distancing measures, and inspire the remainder of the population to receive the vaccine as it becomes available. This requires a logical, compelling, rational argument that is communicated in an approachable manner.

There are three types of rhetoric: epideictic, forensic, and deliberative. The type of rhetoric is dependent upon the focus and purpose of the argument. Epideictic is largely ceremonial and focuses on large audiences.[189] Epideictic rhetoric argues to honor or condemn actions that are currently happening.[190] Forensic-rhetoric is directed towards judges to establish guilt or innocence.[191] Forensic rhetoric is also called the rhetoric of adjudication and appeals to justice for events that have already occurred.[192] Deliberative rhetoric is directed at those who must decide a course of action. The main arguments in deliberative rhetoric are prudence and utility.[193] The conclusions of the arguments made in deliberative rhetoric can be tested by the outcomes they cause. This section will focus mainly on deliberative rhetoric as this is the type of rhetoric that is most applicable to policymaking.

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[189] Rorty, "The Directions of Aristotle's 'Rhetoric,'" 67-68.

[190] Daniel N. Robinson, "Rhetoric and Character in Aristotle," *The Review of Metaphysics* 60, no. 1 (September 2006): 3–15, 8.

[191] Rorty, "The Directions of Aristotle's 'Rhetoric,'" 67-68.

[192] Robinson, "Rhetoric and Character in Aristotle," 8.

[193] Robinson, "Rhetoric and Character in Aristotle," 8.

Rhetoric has been taught since the early Hellenistic times and is still found in universities today as the Socratic method.[194] Rhetoric was developed in parallel by Socrates and Plato. Socrates developed rhetoric as a school of citizenship to train men in moral and political issues to "speak well and have good thoughts."[195] Plato sought a more scientific approach to understanding the "varieties of the human mind; he must understand what sort of argument is convincing to what sort of audience and he must know how to recognize in real life the moment such-and-such rule ought to be applied."[196] Over time, rhetoric has embraced the approaches of both Plato and Socrates. The rhetorician's skill set recommended by this project embraces both approaches as well as encouraging parties to develop and articulate arguments using evidence.

A successful rhetorical argument is able to influence the thoughts and desires of the audience as both factor into decision-making.[197] There are three main parts to the rhetorical argument, content, arrangement, and style.[198] Content, classically referred to as *inventio,* refers to the discovery of what needs to be said to prove an argument.[199] This can be approached in three ways, an inquiry into fact, approach by definition, and approach by quality.[200] Inquiry into a fact questions whether an event did or did not occur or should occur in the future. Approach by definition inquires as to if the actions met a prescribed criterion. Approach by quality inquires as to if the definition is truly correct given the circumstances. The second part, the arrangement of the argument, requires that

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[194] D. A. Russell, "Rhetoric and Criticism," In *Oxford Readings in Classical Studies*. Ed. Andrew Laird, 267–83, 274. Oxford: Oxford, 2006.

[195] Ibid., 270.

[196] Ibid., 270.

[197] Rorty, "The Directions of Aristotle's 'Rhetoric,' 71-72.

[198] Russell, "Rhetoric and Criticism," 274.

[199] Russell, "Rhetoric and Criticism," 273.

[200] Russell, "Rhetoric and Criticism," 274.

the argument flows correctly from one point to another. Finally, the style of the argument is the correctness, clarity, and propriety of the words used.[201] Style includes the use of individual words and the organization of the words but also the use of "figures."[202] Figures are "abnormal configurations of thoughts or words" such as the rhetorical question or the trope.[203] Aristotle gave three parts to the rhetorical argument, *ethos*, *pathos*, and *logos*.[204] These three parts address all potential aspects of decision making, the emotional, the logical, and the human element of trust. Ethos is the credibility and trustworthiness of the speaker. *Pathos* is the emotional appeal of the argument, understanding and addressing the needs and desires of the audience. *Logos* is the content and organization of the argument. The successful combination of these elements allows the rhetorician to establish credibility, intelligence, and character with the audience.[205]

The rhetorician requires intellectual abilities that support practical reasoning and deliberation about facts, choices, and actions.[206] Aristotle's rhetorician embodies virtue. Virtue involves doing the right thing at the right time in the right way for the right reason, which merges the intellectual abilities and character virtues of the rhetorician with "true understanding; and his understanding of the issues at stake in persuasion is formed by appropriately formed desires."[207] In *Nicomachean Ethics,* Aristotle extolled intellectual and moral virtue as the two main types of virtues required for the rhetorician to have good thoughts that result in good actions. For the purpose of this section, I will focus on

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[201] Russell, "Rhetoric and Criticism," 275.
[202] Ibid.
[203] Ibid.
[204] Rorty, "The Directions of Aristotle's 'Rhetoric.' 71-72.
[205] Ibid.
[206] Amelie Rorty, "Aristotle on the Virtues of Rhetoric." *The Review of Metaphysics* 64, 2(June 2011): 715–33, 723.
[207] Rorty, "Aristotle on the Virtues of Rhetoric," 716.

intellectual virtue of which there are six traits. Scientific knowledge requires not just knowing the results but how the results were obtained, and a true understanding of the process used to obtain the results.[208] Knowledge of art is the creation of things, including the process.[209] Intuitive reasoning is the knowledge of the principles from which science proceeds.[210] Wisdom is scientific knowledge combined with intuitive reasoning.[211] I would argue that practical wisdom is the most important intellectual virtue, and also potentially the most difficult to obtain. Practical wisdom is the knowledge of "how to secure the ends of human life," understanding and deliberating what makes a good life for both themselves and society.[212] There is no class or apprenticeship that teaches practical wisdom; it is gained through experience and openness to learning. This is not scientific knowledge nor knowledge of art but an ability to act in accordance with the increasing of human good. The final trait, political wisdom, is the understanding the relations between practical wisdom and political science, requires the prior five be in place. Political wisdom is action and deliberation for a decree to carry out the individual action.[213]

The rhetorician has no specialized subject matter and instead relies upon the work of experts while crafting his or her arguments. This lack of a specialized subject matter that makes the skills of a rhetorician so valuable in policymaking, specifically in target-population recommendations, because it allows the rhetorician to fully consider a

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[208] Aristotle, *The Nicomachean Ethics*. eds. J.O. Ackrill, and J.L. Urmson. Oxford World's Classics. New York, New York: Oxford University Press, 1998, 141.
[209] Ibid., 141.
[210] Ibid., 145.
[211] Ibid., 146.
[212] Ibid., 142.
[213] Ibid., 147.

comprehensive program of evidence, evaluate that evidence, and form a rational, logical argument. The lack of specialized subject matter does require that high-quality evidence from experts be available for the rhetorician to use to craft their argument, further contributing to the importance of evidence evaluation and communication of research which will be discussed in later chapters.

The skill set of the rhetorician is built upon a broad intellectual foundation including studies in the humanities, science, and policy. While the rhetorician has not specialized expertise the intellectual skills to comprehend a wide variety of topics, including the sciences, is needed. The rhetorician's skill set has three main components: logic, reasoning, and communication. Logic is the ability to comprehend the impact of actions and how actions interrelate and impact others. Reasoning is the ability to build an argument in support of the position; as well as the ability to understand and accept alternative points of view and adjust the position as warranted. Communication skills allow the argument to be presented in a comprehendible manner to any audience. This includes the ability communicate over a broad range of topics, articulating a logical, cohesive argument while also engaging other parties in meaningful dialogue in identifying and addressing all sides of the issue. While rhetoric has fallen out of favor, I argue the rhetorician's skill set is essential to vaccine policymaking. The rhetorician's skill set can be used by policymakers to communicate the target-population recommendations to the public better, engage in dialogue to determine barriers to vaccination, and utilize research to articulate logical, appropriate arguments to address concerns. However, rhetoric is not the strict jurisdiction of policymakers. The rhetorician's skill set can, and arguably should, be used by any group to improve

communication and better articulate needs. The rhetorician's skill set is already being successfully utilized by the anti-vaccine movement, although possibly not purposefully. They have their argument well-planned (my child was normal before the vaccine and now isn't), speakers with pathos and ethos that more than compensates (in the media ad for the rest of the public) for the lack of scientific evidence and rationality of the argument. Even when a parent admits they do not know how the vaccine supposedly injured their child, or even what the injury was, being able to time the change in the child to the vaccination is cited as evidence to the lay public. Mothers, especially upper-middle class Caucasian mothers, have a surprising amount of influence with the public. While the rhetorician's skill set can be used by and with any group, parents are a key audience for the discussion on vaccine use. Using the rhetorician's skill set to determine the concerns of the vaccine hesitant and appropriate evidence to sway them will allow policy to be shaped to overcome those concerns; increasing vaccination rates and reducing the burden of influenza.

POLICYMAKING

Policymaking is "a constant struggle over the criteria for classification, the boundaries of categories, and the definition of ideals that guide the way people behave."[214] Deborah Stone's *Policy Paradox* discusses the process and challenges of policy-making in a democratic society. She introduces a model of policy analysis that "recognizes the dark, self-interested side of the political conflict but also sees politics as a

[214] Deborah Stone, *Policy Paradox*: The Art of Political Decision Making, (New York: W.W. Norton & Company, 2012), 9.

valuable creative process for social harmony."[215] I have chosen Stone's model because I believe it is well-suited to health care and is approachable for both scholars and the lay public alike. A caveat to Stone's work, which also applies to this section, is the presentation; Stone's book is laid out as though policymaking occurs in a straightforward, linear fashion; this is rarely the case, the steps of policymaking can occur in any order or concurrently. I believe policymaking will be improved with the incorporation of the rhetorician's skill set.

Goals

The goals of policy must be explicit and precise in order to be implemented and evaluated for success.[216] Goals cannot be considered in isolation; they have practical and ethical implications. Policymakers must navigate these implications, limitations, and interactions of the goals in negotiation with the available resources. Stone lists five broad goals for policies: equality, efficiency, welfare, liberty, and security. Equality goals often consider the distribution of services and other benefits. Questions of distribution are based upon a wide variety of factors with one of the strongest arguments being need and merit; conflicts occur when sides have differing opinions on fairness.[217] From a philosophical standpoint, equality is more complex than allocation. Equality is a human rights issue. Equality comes in many forms: equality of access, equality of opportunity and equality of person, as a few examples. Pure equality often rules afoul of distributive justice, especially in healthcare. In this project, I use equality to mean equality of access

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215 Ibid., 10.
216 Ibid., 251.
217 Ibid., 40.

which, in order to be just, must be absolute unless evidence supports inequality to assure equality of outcomes.[218] Efficiency goals focus on reducing waste from duplication and inappropriate use of resources. Although efficiency is often an economic consideration, I take efficiency to mean not wasting valuable resources. These resources can be time, money, services, and most of all human life. Welfare concerns health and wellbeing of society and the individual members. According to Stone, "because the need is such a strong moral claim, the question of what people need for their welfare strongly influences larger debates about what government should strive to provide for its citizens."[219] Needs must be met reliably and securely over time.[220] States have legislative authority to pass laws to regulate the wellbeing of their residents. Liberty and security goals are particularly compelling because they are vaguely defined. Liberty is most often described as the government not interfering in individual actions.[221] Liberty can also be defined as the freedom to take certain action without fear of retaliation or harm. Security goes hand-in-hand with liberty. Security can mean a variety of different things: financial security, physical security, being secure in having liberties.

Goals must balance both desire and needs. Rorty refers to this as the rhetorician's need to address "real interests, and not merely their surface desires" of the audience.[222] Classic rhetorician's had the somewhat similar task of balancing the interests and desires

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[218] The ethical justification of the target-population recommendations will be discussed in chapter five.

[219] Ibid., 85. Stone uses Abraham Maslow's Hierarchy of needs to support the discussion of welfare goals. People require the following needs be satisfied in order: physiological needs such as hunger and thirst, then safety and shelter, followed by social needs such as companionship, self-esteem, and finally self-actualization.

[220] Ibid., 86-87.

[221] Stone, Policy Paradox, 109.

[222] Rorty, 1992, 65.

of a much smaller audience than modern policymakers, but the sentiment is the same. Everyone wants vaccines that are 110% effective, 150% safe, and cost a dollar but that is not a possibility.[223] Using the rhetorician's skill set to discover what is acceptable to the public and feasible to accomplish allows those discoveries to be implemented as policy. Vaccine policy must balance liberty and security goals; while the best way to prevent infections (providing security) would be compulsory vaccinations the public outcry over the loss of personal choice and invasion of individual liberty would be great. Thus, vaccine policy provides recommendations for who is at most risk and preserves the ability for all populations to make a choice concerning vaccination. Goals present the ideal; through the political process goals are compared with problems, weighed against reality and eventually, a solution is reached.

Problems

Problem definition is neither an easy nor straightforward task because "[t]o define an issue is to make an assertion about what is at stake and who is affected and therefore, to define interests and reconfigure alliances. There is no such thing as an apolitical problem definition."[224] Stone outlines four ways that problems are brought to the attention of policymakers and the public: symbols, numbers, causes, and interests.[225]

Symbols are powerful tools in illustrating problems being "especially persuasive because their story lines are subtle and their poetry so emotionally compelling that the

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[223] Alan Barrett. "How Do You Test a Vaccine Against Zika?" IMH Brown Bag. Institute for the Medical Humanities. Galveston. July 13, 2016.

[224] Stone, *Policy Paradox*, 247.

[225] Ibid., 229. Interest groups are organizations made up of people affected by specific issues or problems and include professional societies, advocacy groups and political organizations.

normative leap slips right past our rational brains."[226] Narrative stories are a symbolic means of defining and contesting problems. One of the reasons the 1918 pandemic is so feared is the narratives that have been left behind. Descriptions of bodies piled in the streets, mass graves and people literally choking to death on their own blood are difficult to brush aside. The link between vaccines and autism will never go away because of the established narrative that has been perpetuated despite repeated scientific evidence disproving the link. Narrative symbols tell a better story than data points ever could, and it is the narrative story that stays with people. Personal narratives negatively impact the public's trust of vaccines. The narrative for vaccines is rarely positive; although the CDC does have a vaccine narrative website to illustrate the burden of vaccine preventable illness. The media rarely reports on good outcomes from vaccines, the headline "Influenza Season Results in Low Death Rate Thanks to Vaccinations" is highly unlikely. While outbreaks of vaccine preventable illness are reported, these reports often contain repetitions of the anti-vaccine narrative as justification for why the vaccine was not used.

Numbers allow problems to be quantified in scope and scale but create a fundamental conflict in how the counting should occur.[227] While categories have to be created, the boundaries of the categories are ripe for contention.[228] Wrongful-inclusion occurs when two things are technically the same but are actually vastly different. Some studies will claim that the influenza vaccine reduces influenza-like illness or acute respiratory infections (known as effectiveness), but efficacy is measured in the reduction of laboratory-confirmed influenza infections. While two studies may show a decrease in

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[226] Ibid., 177.
[227] Ibid., 183.
[228] Ibid., 186.

an upper respiratory illness, only one actually measures how efficacious the vaccine is against the targeted virus. Using numbers to define a problem can also falsely inflate the severity of the problem by asserting that it common enough to bother counting and that the phenomenon can be both easily identified and counted.[229] Numbers are also easy to manipulate and create a sense of power and authority in those using the numbers to support their claims.[230] Understanding the scope of a problem is critical to drafting good policy and having an accurate numeral value is a portion of the understanding.

Policy problems are inherently subjective and politically-based. Every group sees the problem from their particular perspective. A challenge to the policymakers is crafting a solution that gets interested parties on the same page and addresses the needs of all interested parties. This is one of the areas which the rhetorician's skill set would benefit policymaking. Deliberative rhetoric is most often used in policymaking because it opens a dialogue regarding a future course of action. Arguments for and against the proposed policy can be crafted using the rhetorican's skills of communication and reasoning. This allows interested parties to make their needs and desires known in order for them to be incorporated into the final policy.

Solutions

Policy addresses the gap between goals and problems by creating rules for society. Rules are shaped by acts and rights, promulgated by the government's legislative authority and enforced using incentives. Trust in the government's reasoning, and the process is also key for compliance in voluntary programs.

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[229] Ibid., 192-3.
[230] Ibid., 201.

Facts create conflict in determining which fact is most accurate and most applicable to the situation.[231] Facts are used as a persuasion tool; in an ideal model, this is done through rational deliberation with individuals "pondering together, weighing, questioning, and eventually, reaching consensus."[232] Unfortunately, facts can be misrepresented and cause confusion. For example, both of the following statements are facts about the influenza vaccine:

> 1: The influenza vaccines can prevent up to 80 percent of influenza infections.
> 2: The 1976 swine influenza vaccine was linked to increased rates of Guillain-Barre syndrome.

Both of these statements have been used outside of their appropriate context to bolster and attack the influenza vaccine. Stating the influenza vaccine prevents 80 percent of influenza infections without clarifying the requirement for a good virus-vaccine match or that the 80 percent is the upper level of prevention overstates the efficacy of the vaccine. Stating that the 1976 vaccine was linked to Guillian-Barre without mentioning that it had not occurred before, or since, implies that the influenza vaccine may cause GBS.

The creation of legal rights is a long-standing impulse in American politics.[233] There are two traditions of rights, the realist and the normative. Under the realist tradition of rights, a citizen's claim to a right is backed by the power of the government. In the normative tradition, rights exist separate from government and derive from some source other than the power of enforcement.[234] An interesting dichotomy of rights is the

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[231] Ibid., 312.
[232] Ibid., 313.
[233] Ibid., 331.
[234] Ibid., 332.

argument of "God-given rights" which may be backed by the government to a limited extent, if at all. The "God-given right" of a parent to raise their child as the parents see fit is only supported by the government to the point that the actions of the parent do not endanger the child. Personal autonomy in medical decisions regarding vaccinations is generally seen as a "God-given right, " but this right was overruled in the *Jacobson v. Massachusetts* case.[235] The Commonwealth of Massachusetts mandated smallpox vaccinations during an outbreak in 1902 under threat of criminal penalty for noncompliance. Jacobson sued to claim that the compelled vaccination was a violation of his 14th Amendment rights. The Supreme Court of the United States ruled that the states could compel vaccination under the state's police power for regulation of the general safety of the public during the outbreak. Neither rights nor facts are absolute.

The purpose of incentives is to bring individual actions in line with community goals. Incentives are based on the utilitarian theory that individuals will do what takes the least effort to meet their desires.[236] Incentives can be positive, such as a reward for certain behaviors, or negative, such as a fine, but must be distributed or enforced in order to be effective. Incentives can create paradoxes by rewarding and punishing at the same time; Stone uses the example of bonuses for workplace safety resulting in retaliation against workers when accidents are reported.[237] Incentives can also cause harm when they are poorly designed, such as when healthcare subsidies are leveraged for compliance.[238] By removing healthcare subsidies for poor compliance, the ability to

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[235] *Jacobson v. Massachusetts*, 197 U.S. 11 (1905)
[236] Stone, *Policy Paradox*, 270.
[237] Ibid., 280.
[238] Ibid., 281.

comply with the rules is negatively impacted. Incentives help increase compliance with rules only when they are well designed and enforced; poorly designed incentives are counter to policy goals and encourage rule-breaking.

Rules provide predictability by ensuring that like cases will be treated the same and insulate citizens from officials. While "a good rule should be precise enough to accomplish its purpose and prevent people from manipulating it in ways that undermine its intent" rules are often purposely vague to allow for flexibility for both the policymakers and in enforcement.[239] Rules (policies) allow society to run more efficiently by making expectations of behavior clear. Influenza policy allows citizens to be aware when and where to get an influenza vaccine, who is eligible to receive the vaccine and how much the vaccine will cost.

Policy problems and solutions can be crafted using a hermeneutical process. The scope of hermeneutics has evolved from interpreting the bible to interpreting all texts, and finally to interpreting human interaction. Like rhetoric, hermeneutics aims to reach mutual acceptance and understanding of a point of view. Hans-George Gadamer's most influential work, *Truth and Method*, was published in 1960.[240] This section will focus on a smaller section of the text, Gadamer's concept of the hermeneutic circle which relates to my discussion on policymaking and parallels rhetoric. Gadamer claims the task of hermeneutics is to "clarify this miracle of understanding, which is not a mysterious

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[239] Ibid., 293, 300.

[240] Jeff Malpas, "Hans-Georg Gadamer," ed. Edward N. Zalta, *The Stanford Encyclopedia of Philosophy*, 2013, ttp://plato.stanford.edu/archives/win2013/entries/gadamer/.

communication of souls but sharing in a common meaning."[241] This common meaning is found not by trying to determine what the author was thinking but what the author's perspective may have been at the time of writing.[242] By sharing the author's perspective, the reader is then able to appreciate the content that the author has shared.

Using the hermeneutic circle in policymaking would allow for the creation of policies that better reflect the needs of citizens and result in more feasible, reasonable solutions by encouraging honest communication and true understanding between parties. The hermeneutic circle is the constant process of developing an understanding based on the interpretation and application of communication and then changing the interpretation and application based upon the new understanding.

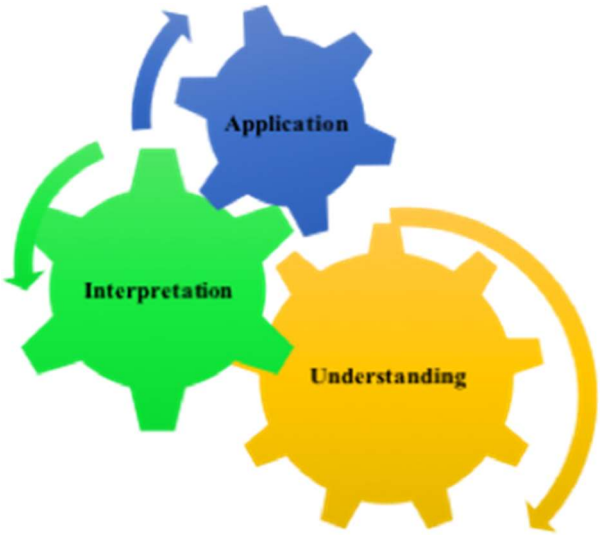

FIGURE 3: HERMENEUTIC CIRCLE

The use of the gear to illustrate the hermeneutic circle is purposeful; the turning of each gear affects the other showing how a change in one impacts the rest. The description of a circle is somewhat deceptive as it implies that the process is smooth and orderly when instead it is dynamic, with each component affecting all others but still working together. It is important to note the interaction between each part of the hermeneutic circle: "interpretation is not an occasional, post facto supplement to

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[241] Hans-George Gadamer, *Truth and Method*, trans. Joel Weinsheimer and Donald G. Marshall, 2nd ed. (New York: Continuum, n.d.).292.

[242] Ibid.

understanding, rather understanding is always interpretation, and hence interpretation is the explicit form of understanding."[243] Correct understanding allows for appropriate application and comes from correct interpretation, but the application can affect understanding and interpretation; thus, the circular impact and representation. Hermeneutics ties to rhetoric as they share a goal of creating common meaning and understanding between the parties. Rhetoric is the construction and delivery of the argument; hermeneutics is the understanding of the argument. The two processes can work together to improve policymaking. Evidence-based policymaking is amenable to the hermeneutical process by incorporating additional resources to allow for deeper understanding between involved parties.

EVIDENCE-BASED POLICYMAKING

Evidence-based policymaking, also called evidence-informed policymaking, seeks to incorporate high-quality research evidence into the legislative process to create more effective policies. This section will address the background and processes of evidence-based policymaking (EBP). The goal of this section is to identify the challenges to implementing evidence-based policymaking for the influenza vaccine.

While political decisions are often justified using social values, research allows those subjective values to be balanced objectively for a complete view of the situation at hand.[244] Under the evidence-based medicine model, evidence is:

> developed through systematic and methodologically rigorous clinical research, emphasizing the use of science while deemphasizing the use of

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[243] Ibid., 307.

[244] Stephen R. Hanney, and Miguel A. Gonzalez-Block, "Evidence-Informed Health Policy: Are We Beginning to Get There at Last?" *Health Research Policy and Systems* 7 (December 2009): 30.

> intuition, unsystematic clinical experience, patient and professional values, and pathophysiologic rationale.[245]

Intuition, unsystematic experiences and values are deemphasized, but not disregarded, because of their inability to be widely applied. While clinical experiences and personal values are critical for individual decision-making, policy decisions need to be made with a comprehensive evidence base. Within clinical research, there are five main types of studies that can be used as evidence: a meta-analysis, randomized controlled trials, cohort studies, case-controlled studies, and cross-sectional studies.[246] Meta-analysis and systematic reviews collate data into one resource and thus are most useful in policymaking. The specific types of research, and how they are evaluated, will be further discussed in chapter four.

Background and Process

Calls for evidence, and rational-based decisions can be traced back to the Enlightenment's turn from religious rhetoric to secularism. The turn from religious rhetoric to secularism has been described as an "intellectual and practical agenda that set aside the tolerant, skeptical attitude of the 16th-century humanist and focused on the 17th-century pursuit of mathematical exactitude and logical rigor, intellectual certainty, and moral purity."[247] This turn from blind religious faith to intellectual certainty gave rise to the rationalist movement. The rationalist movement had three goals: "a rational

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[245] Mark J Dobrow, Vivek Goel, and R. E. Upshur, "Evidence-Based Health Policy: Context and Utilization." *Social Science & Medicine* 58, no. 1 (January 2004): 207–17, 207. doi:http://dx.doi.org/10.1016/S0277-9536(03)00166-7.

[246] Laurie K. Twells, "Evidence-Based Decision-Making 1: Critical Appraisal*." Methods in Molecular Biology* 1281 (2015): 385–96, 393. doi:10.1007/978-1-4939-2428-8_23.

[247] Stephen Toulmin. *Cosmopolis.* Chicago IL: University of Chicago Press, 1990, x.

method, a unified science, and an exact language to unite all."[248] In the 20th century, reformers sought to 'render policy more scientific and less political by removing policy-making authority from elected bodies and giving it to expert commissions and professional city managers."[249] While the goal to "prevent ideological and theological issues from confusing matters, both the intellectual and the practical means of improving the human lot" was admirable, we are still attempting to find a way to meet this goal two centuries later.[250] Evidence-based policy is one of the ways that we have sought to prevent ideology from overtaking policymaking. EBP represents an avenue where humanities education and skills in rhetoric are becoming more valuable in the modern age. Humanists have traditionally received extensive training in rhetoric and honed the ability to argue both sides of an argument while staying outside of the political regime out of loyalty to the system and public as opposed to the ruler.[251]

Evidence-based policy seeks to incorporate research into the policy-making process to "ensure that decision making is well-informed by the best available research evidence."[252] Research can be used in policymaking in three ways. First, research can prove that a problem does in fact exist. Second, research can show the extent of a known or suspected problem. For example, a concern of live attenuated influenza vaccines is the possibility of exacerbating wheezing in children with asthma; research is in progress to

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[248] Toulmin. *Cosmopolis.* 104.
[249] Stone, *Policy Paradox,* 9.
[250] Toulmin. *Cosmopolis*, 3.
[251] James Hankins. "Humanism and the origins of modern political thought." *The Cambridge Companion to Renaissance Humanism*, ed. Jill Kraye (Cambridge, UK: Cambridge University Press, 1996), 118-141, 122.
[252] Andrew Oxman, John N. Lavis, Simon Lewin, and Atle Fretheim. "Support Tools for Evidence-Informed Health Policymaking (STP) 1: What Is Evidence-Informed Policymaking?" *Health Research Policy and System* 7, Suppl 1 (December 2009): S1.

confirm or deny this concern Research clarifies problems by comparing incidence rates in similar areas and evaluating potential solutions.[253]Defining the problem requires the determination of the duration and burden of the problem as well as the scope of the impact; these help00 set the priority for addressing the problem. Finally, research can be used to evaluate proposed or existing policies by providing policymakers valuable insight into the impacts of options and help narrow solutions.[254] Evidence, utilized well, can be a powerful political tool.

Research must be made available to policymakers in a timely manner in order to have an impact on policy. The use of clinical research by policymakers is a secondary utilization; clinical research is rarely commissioned specifically for policymakers. The "stock or reservoir of knowledge" is fed by researchers and practitioners and exploited by policy makers through systematic reviews and public engagement.[255] There are four methods used to provide information to policymakers. *Push-efforts* aim at delivering evidence to policymakers, outside of specific requests, through evidence briefs.[256] *Pull-efforts* attempt to encourage policymakers to proactively seek out, assess, adapt, and apply research.[257] *Exchange-efforts* are a combination of push and pull efforts into a collaborative process between researchers and policymakers using evidence-briefed

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[253] John N. Lavis, Michael G Wilson, Andrew D Oxman, Simon Lewin, and Atle Fretheim. "SUPPORT Tools for Evidence-Informed Health Policymaking (STP) 4: Using Research Evidence to Clarify a Problem." *Health Research Policy and Systems /* BioMed Central 7 Suppl 1, no. 1 (January 16, 2009): S4. doi:10.1186/1478-4505-7-S1-S4.

[254] Ibid.

[255] Stephen R Hanney, Miguel A Gonzalez-Block, Martin J Buxton, and Maurice Kogan. "The Utilization of Health Research in Policy-Making: Concepts, Examples and Methods of Assessment." *Health Research Policy and Systems* 1 (2003): 2. doi:10.1186/1478-4505-1-2.

[256] Fadi El-Jardali, John Lavis, Kaelan Moat, Tomas Pantoja, and Nour Ataya. "Capturing Lessons Learned from Evidence-to-Policy Initiatives through Structured Reflection." *Health Research Policy and Systems* / BioMed Central 12 (2014): 2. doi:10.1186/1478-4505-12-2.

[257] Ibid.

informed dialogues.[258] Research is more likely to be used through the gradual exposure of insight, theories, and concepts known as the limestone model.[259] All of these methods suffer from a lack of resources and training for utilization.

Argumentation is another process used to integrate evidence into policymaking. The process of argumentation has its basis in rhetoric.[260] Aristotle's rhetoric has three dimensions, the logos (argument and evidence), the ethos (credibility of the speaker), and the pathos (appeal to emotion).[261] The process of argumentation used in EBP does not put much weight to the ethos or pathos dimensions, which is reflective of an overall critique of EBP- the lack of human context. Argumentation uses dialogue in a structured approach to resolve the conflict.[262] Available data are used to discuss the issue with a warrant (the rule used to justify the data) via deductive reasoning.[263] For example, the data point that "Socrates is a mortal is warranted by the statement that all men are mortal; Socrates is a man and therefore mortal."[264] If the warrant is challenged, it is then backed with additional data. Inductive reason is used to establish warrants.[265] The rebuttal portion of the discussion involves factors that limit the validity of the claim or conclusion.[266] Data and information have distinct functions when they are presented as evidence; they can be the foundation for the conclusion or justification for the warrant.[267]

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[258] El-Jardali, et al., "Capturing Lessons Learns from Evidence-to-Policy Initiatives"
[259] Hanney, et al. "The Utilization of Health Research in Policy-Making".
[260] Trisha Greenhalgh, and Jill Russell. "Evidence-Based Policymaking: A Critique." *Perspectives in Biology and Medicine* 52, no. 2 (2009): 304–18, 313. doi:10.1353/pbm.0.0085.
[261] Greenhalgh, "Evidence-Based Policymaking: A Critique." 313.
[262] Dickinson, "Evidence-Based Decision-Making: An Argumentative Approach" 74.
[263] Dickinson, "Evidence-Based Decision-Making: An Argumentative Approach" 75.
[264] Dickinson, "Evidence-Based Decision-Making: An Argumentative Approach" 75.
[265] Dickinson, "Evidence-Based Decision-Making: An Argumentative Approach" 76.
[266] Dickinson, "Evidence-Based Decision-Making: An Argumentative Approach" 76.
[267] Dickinson, "Evidence-Based Decision-Making: An Argumentative Approach" 78.

Research evidence is warrant-establishing, not warrant using; this is a common misunderstanding in evidence-based decision making.[268] The clinical evidence supporting the target-population recommendations would be the warrants for influenza vaccine policy. For example, the statement "the influenza vaccine is safe and effective in healthy adult populations" would be warranted with the data that very few associations of multiple sclerosis, optic neuritis, or Guillain-Barre syndrome were made between the seasonal inactivated influenza vaccine and the vaccine was effective in reducing influenza symptoms in the general population.[269]

Despite the wealth of information available, there will be times that there will be an insufficient amount of research to support a particular policy.[270] This may be due to lack of communication between policymakers and researchers regarding the types of information needed or a lack of resources to access available information. Care must be taken not to confuse the lack of systematic reviews with the lack of evidence, and the inconclusive evidence with no effect as these do not necessarily indicate a lack of evidence but a degree of uncertainty which must be acknowledged.[271]

Critiques of Evidence-Based Policy

Evidence-based policy is a well-regarded ideal but a critiqued practice. Evidence-based policy has been reduced to a scientifically based rational decision model by naive

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[268] Dickinson, "Evidence-Based Decision-Making: An Argumentative Approach" 79.

[269] Thomas Jefferson, Carlo Di Pietrantonj, Alessandro Rivetti, Ghada A. Bawazeer, Lubna A. Al-Ansary, and Eliana Ferroni. "Vaccines for Preventing Influenza in Healthy Adults." Co*chrane Database Systematic Reviews,* no. 7 (July 2010): CD001269.

[270] Andrew D. Oxman, John N Lavis, Atle Fretheim, and Simon Lewin. "SUPPORT Tools for Evidence-Informed Health Policymaking (STP) 17: Dealing with Insufficient Research Evidence." *Health Research Policy and Systems* / *BioMed Central* 7 Suppl 1, no. 1 (January 16, 2009): S17. doi:10.1186/1478-4505-7-S1-S17.

[271] Ibid.

proponents: "the making of a policy decision is seen as technical, logical process comprising the selection, synthesis, and critical evaluation of best research evidence, from which the obvious (or at least, a preferred) answer to a particular policy problem will emerge."[272] Evidence-based policy can come dangerously close to assuming that ethical and moral issues can be reduced to questions of rationality and evidence.[273] No matter how high the quality, evidence alone cannot determine an answer. Another critique of evidence-based policy is the devaluation of the democratic process and marginalization of professional experience and tacit knowledge.[274] By relying too heavily on evidence and rationality, it is feared that policy will lose sight of its purpose to help improve society for the benefit of the people who live in it.

Challenges in Evidence-Based Policymaking

As previously stated, research utilization suffers from mutual distrust and lack of communication between researchers and policymakers and a lack of relevant and readily available research. [275] In short, policymakers do not know what researchers have to offer, and researchers do not understand the specific needs of policymakers. This is not to claim that policymakers do not utilize research, only to state that some are more likely than others to do so. Administrative decision-makers with specialized knowledge, such as

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[272] Trisha Greenhalgh, and Jill Russell. "Evidence-Based Policymaking: A Critique." *Perspectives in Biology and Medicine* 52, no. 2 (2009): 304–18, 305. doi:10.1353/pbm.0.0085.

[265] Nick Black. "Evidence Based Policy: Proceed with Care." *BMJ (Clinical Research Ed.)* 323, no. 7307 (2001): 275–79. doi:10.1136/bmj.323.7307.275.

[274] Greenhaulgh, "Evidence-Based Policymaking: A Critique." 305.

[275] Simon Innvaer, Gunn Vist, Mari Trommald, Andrew Oxman, and S Innvaelig. "Health Policy-Makers Perceptions of Their Use of Evidence: A Systematic Review." *Journal of Health Services Research and Policy* 7, no. 4 (2002): 239–44 ST – Health policy – makers perceptions of. doi:10.1258/135581902320432778.

those on advisory boards, will often seek out research to assist with decision making.[276] Administrative decision-makers are also more likely to have personal ties to researchers and contacts to call upon with questions or requests for information.[277] Legislative decision makers, such as an elected members of Congress, often do not have a specific tie to research and are less likely to be aware of its existence on a particular issue.[278] Additionally, legislative decision makers will generally be more receptive to research findings that have been distilled into short memos that are free of technical jargon.[279] Unfortunately, researchers often do not disseminate their findings in ways that are readily accessible to those outside the scientific community.[280]

Policymakers often lack resources and training to find and evaluate high-quality clinical research. Policymakers tend to cite anything that is not personal experience or anecdotes as 'evidence,' illustrating a need for education.[281] Research is inaccessible to policymakers. Often the article is unavailable; the data is too specific, or the policymaker is unable to assess the quality and applicability of the conclusions.[282] When policymakers are able to access research, they are often unsure of how to apply it within the policymaking process.[283] Inaccessibility to research combined with the need to make decisions quickly and prior policy promises leads to decisions made with so-called

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[276] Lomas, "Research and Evidence-Based Decision Making", 439.
[277] Ibid.
[278] Ibid.
[279] Ibid.
[280] Lomas, "Research and Evidence-Based Decision Making", 439.
[281] Lesley Wye, et al., "Evidence Based Policy Making and the 'Art' of Commissioning - How English Healthcare Commissioners Access and Use Information and Academic Research in 'Real Life' Decision-Making: An Empirical Qualitative Study." *BMC Health Services Research* 15, no. 1 (January 29, 2015): 430. doi:10.1186/s12913-015-1091-x.
[282] Christopher J. Jewell, and Lisa A Bero. "'Developing Good Taste in Evidence': Facilitators of and Hindrances to Evidence-Informed Health Policymaking in State Government." *The Milbank Quarterly* 86, no. 2 (June 2008): 177–208, 188-189. doi:10.1111/j.1468-0009.2008.00519.x
[283] Wye, et al. "Evidence Based Policy Making and the 'Art' of Commissioning."

common sense, gut reactions, and standards of practice.[284] A United Kingdom study from 2011 to 2013 revealed four conclusions regarding research access and utilization in policymaking.[285] First, volumes of research are produced each year, but very few published studies are relevant to policymakers.[286] Second, peer-reviewed articles are largely inaccessible to policymakers due to high access cost and jargon.[287] Third, research methods used to provide generalizable data sacrifice desired local context.[288] Finally, researchers make little effort to understand the context policymakers work in and adjust research outputs. This results in policymakers being unable to utilize research in a meaningful manner.

Evidence-based vaccine policy faces an additional set of challenges. Dr. Tom Jefferson, an influenza epidemiologist, published a critique of influenza vaccine policy in a 2006 *British Medical Journal* article claiming that systematic reviews do not provide accurate or adequate information regarding influenza vaccine's efficacy in key populations.[289] Jefferson pointed out three issues with evidence in influenza policy: 1) over-reliance on non-randomized controlled trials, 2) absence of information for target-populations and 3) the small, heterogeneous safety dataset for influenza vaccines.[290] While Dr. Jefferson has changed his stance since then, publishing multiple systematic reviews with the Cochran Library, he was correct to point out that influenza vaccine

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[284] Jewell, and Bero. "'Developing Good Taste in Evidence," 184.
[285] Wye, et al. "Evidence Based Policy Making and the 'Art' of Commissioning."
[286] Ibid.
[287] Ibid.
[288] Ibid.
[289] Tom Jefferson, "Influenza Vaccination: Policy versus Evidence." BMJ *: British Medical Journal* 333, no. October (2006): 912–15. doi:10.1136/bmj.38995.531701.80.
[290] Ibid., 913.

research is difficult to study in a randomized, controlled manner. Randomized controlled trials are the gold standard in clinical research, which presents a challenge to vaccines:

> A well-conducted prospective survey or case-control study may very well be all that we have to examine a question and a well-conducted prospective survey may success where a poorly run randomized clinical trial would fail. Restricting a systematic review of only RCTs often ignores the breadth of studies and data available and may very well suggest that a vaccine's efficacy and safety are insufficiently substantiated.[291]

Randomized controlled trials are difficult in vaccine research due to cost, ethical concerns, and practicality.[292] The types of research that target-population recommendations are based upon will be further evaluated in chapter four. The main challenge to evidence-based vaccine policy is the "lack of a clear understanding of policy objectives and the availability of relevant measurement instruments."[293]

While the evidence-based policy is challenging, the results are impressive. Mexico's experience in healthcare reform is an example of a successful evidence-based policy. While Mexico introduced social insurance in 1943, coverage had been limited to salaried employees in private firms and public sector employees.[294] By 2000, only half of Mexican families had insurance and those who did not were mainly the poor. This left the most vulnerable without a social safety net. Further analysis showed that in the first trimester of 2000 almost 1.5 million household were either driven below or pushed

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[291] Robert M. Jacobson, Paul V. Targonski, and Gregory A. Poland. "Why Is Evidence-Based Medicine so Harsh on Vaccines? An Exploration of the Method and Its Natural Biases." *Vaccine* 25, no. 16 SPEC. ISS. (2007): 3165–69, 3168-69. doi:10.1016/j.vaccine.2007.01.049.

[292] Ibid., 3166.

[293] Louis W. Niessen, Els W.M Grijseels, and Frans F.H Rutten. "The Evidence-Based Approach in Health Policy and Health Care Delivery." *Social Science & Medicine* 51, no. 6 (2000): 859–69, 862. doi:10.1016/S0277-9536(00)00066-6.

[294] Julio Frenk. "Bridging the Divide: Global Lessons from Evidence-Based Health Policy in Mexico." Lancet 368, no. 9539 (2006): 954–61, 955.

deeper into poverty due to a health-related expenditure.[295] These analyses, combined with a WHO assessment of health-system fairness, in which Mexico ranked poorly, led to a detailed country-level analysis on the status of the health care system.[296] This evidence was used to promote major legislative reform that was approved by a large majority of all political parties.[297] Starting January 1, 2004, Popular Health Insurance gradually enrolled 12 million families with the goal of universal coverage by 2010.[298] By 2006, Mexico had reduced the number of families driven into poverty by medical expenditures by a third.[299] Julio Frenk, the Minster of Health for Mexico, who designed and implemented the health care reform stated: "[t]he path is clear: sound evidence must be the guiding light for designing, implementing, and evaluating programs in national governments, bilateral aid agencies, and multilateral organizations. This is the path that will lead to more equitable development through better policy making for health."[300] Mexico leveraged research evidence to determine the problem in their health system, the populations most affected, and whether, the policy was effective at meeting its goals

I see the ideal evidence-based policymaking process embracing the hermeneutical circle, and rhetorical skills discussed earlier in this chapter. While high-quality evidence is critical to effective policy; evidence-based policy risks sacrificing human values by strict reliance on evidence. The assumption that ethical and moral issues can be reduced to questions of rationality and evidence can be circumvented by embracing human

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[295] Ibid.
[296] Ibid., 956.
[297] Ibid., 956.
[298] Ibid., 956. Popular Health Insurance is a public, voluntary service funded by increasing the allocation from federal and state contribution and readjusting the percentage of gross domestic product spent on health and welfare; most importantly it is affordable and sustainable for a developing country
[299] Ibid., 958.
[300] Ibid., 960.

experiances; leading to a better policy that improves the lives of the citizens it is meant to serve.

Integrating research into policymaking is difficult because it requires a change in custom for both policymakers and researchers. Montaigne noted the power of custom as a

> violent and treacherous schoolmistress. She by, little and little, slily [sic] and unperceived, slips in the foot of her authority, but having this gentle and humble beginning, with the benefit of time, fixed and established it, she then unmasks a furious and tyrannic countenance, against which we have no more the courage or power so much as to lift up our eyes. [301]

Changing the processes used to make policy and communicate science is a difficult task because they have become customs of everyday life for researchers and policymakers. Therefore, changes must be made incrementally and continually reinforced to become new customs.

Successfully implementation of evidence-based policy requires the integration of science and policy in addition to communication plans and the consideration of ethical implications. A broad, humanist education would be beneficial, but not necessarily required, to those seeking to assist in this process. In an age where education is becoming ever more specialized and the timelines for graduation shortened while the requirements are increased, the traditional humanities education is no longer be valued. Montaigne once criticized the process of university education by not requiring students to understand and analyze the material "to know by rote is no knowledge and signifies no more but only

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[301] Michel de Montaigne, "Of Custom, and That We Should Not Easily Change a Law Received " (Book 1, chap. 22); in *Essays of Michel de Montaigne,* trans. Charles Cotton (1685), ed. William Carew Hazlitt (1877), Project Gutenberg Ebook #3600 (September 17, 2006), http://www.gutenberg.org/files/3600/3600-h/3600-h.htm;

to retain what one has entrusted to our memory."[302] Unfortunately, this has not changed and one of the challenges to evidence-based policy; because we are no longer taught to understand and interpret material it is difficult to bring the gap between disciples.

Unsurprisingly, the best solution is increased communication between researchers and policymakers. Jonathan Lomas addressed this need in 1997 when he suggested the creation of a new role within healthcare, the knowledge broker.[303] According to the Lomas, the knowledge broker would be trained in both research and decision-making skills acting " as a bridge between the two communities, able to translate the opportunities, constraints, and findings from one setting to the other." The knowledge broker would benefit from the skills of the classic rhetorician and humanities to successfully fulfill this task. The knowledge broker is an interesting title for the person responsible for utilizing the rhetorician's skill set. Somewhat egotistically, I could easily argue that I am the ideal rhetorician for the influenza vaccine debate. I am familiar with both the science and the policymaking aspects. I am intimately familiar with the personal impacts of the influenza virus. I am the caregiver for my disabled mother who is a member of the target-populations. I have a nine-month old goddaughter that I love more than anything in the world. I have been hospitalized due to influenza twice. I can make the arguments for, and against, the influenza vaccine as a caregiver, daughter, and an informed member of the public. Would my argument as someone who depends on the vaccine to protect her disabled mother and infant godchild defeat those of a mother who

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[302] Michel de Montaigne, "Of the Education of Children" (Book 1, chap. 25, 1579-80); in *Essays of Michel de Montaigne*, trans. Charles Cotton (1685), ed. William Carew Hazlitt (1877), Project Gutenberg Ebook #3600 (September 17, 2006), http://www.gutenberg.org/files/3600/3600-h/3600-h.htm;

[303] Lomas, "Research and Evidence-Based Decision Making", 440.

believed her child to be injured by a vaccine or Ms. Kiney who contracted GBS after receiving the 1976 Swine Flu Vaccine; likely no but it would move the conversation in the right direction. One of the problems with the rhetorician's skill set is that it relies on free will and people being open to having the dialogue. It will only be through the sysematic and consistent communication of accurate information that change will occur. I will be just one of the knowledge brokers utilizing the rhetorician's skill set to make that change.

Conclusion

This chapter reviewed how the rhetorician's skill set could be used to improve and facilitate vaccine policy. Facilitating the integration of high-quality clinical research improve communication and decision making regarding influenza vaccine policy. The rhetorician's skill set can be applied in three ways. These three general applications of the rhetorician's skill set are specifically leveraged during the policymaking process. Goals must balance the needs and desire of multiple stakeholders. The rhetorician facilities this by helping stakeholders build rational, logical arguments supporting their needs with appropriate evidence and communication these arguments in an understandable manner. Policy problems and solutions can be designed using a hermeneutical process which I argue is closely aligned with rhetoric. Hermeneutics and rhetoric both promote honest communication and understanding between the parties. Rhetoric is the art of making the communicating the argument; hermeneutics is the application and integration of the argument. Utilizing the rhetorician's skill set within the evidence-based policymaking process allows for better communication between researcher, policymakers, and the public regarding policy decisions. The rhetorician's skill set is not a quick fix and is more

of a general recommendation than a point-by-point plan. Completion of a fully executable plan of action is a future direction of this project. Improving the quality of communication may not only result in better policy but also increase public trust in both the target-population recommendation and the influenza vaccine leading to improved public health.

Chapter Three: Analysis of the Recommendations

The influenza virus causes seasonal epidemics and unpredictable pandemics that can be managed with the assistance of the influenza vaccine, as discussed in prior chapters. Policy is required to manage the distribution of vaccine supplies in the event of a shortage. Target-populations represent the groups considered to be at the highest risk of suffering from severe illness and complications such as hospitalization and premature death from infection with the influenza virus. The recommendations state that these populations should receive the influenza vaccine every year and receive priority in the event of a vaccine shortage. The World Health Organization issues the target-population recommendations on a global level which are meant to be customized to each nations' need and resource level. The Centers for Disease Control and Prevention issue the yearly recommendations for the influenza vaccine in the United States, which include the target-populations. The target-populations are significant for two reasons. First, the recommendations create de facto priority even when vaccine supplies are plentiful. This de facto priority is created by identifying the populations as high-risk and the marketing of vaccination campaigns to theses populations. Second, the recommendations create actual priority when vaccine supplies are scarce. Vaccine scarcity can occur due to manufacturing issues impacting supply or a pandemic requiring a new vaccine to be developed. Due to this de facto and actual prioritization, it is imperative that the target-population recommendations be created using a transparent and ethical process while also being based on high-quality research. This chapter focuses on the processes used to create the recommendations and the recommendations themselves.

This chapter will be divided into two parts. The first will provide an exploration of the process used by the WHO and CDC to create the target-population recommendations. The purpose of this exploration is to determine the process used by the WHO and CDC in comparison to the general policymaking framework discussed in chapter two. This will allow for potential areas of improvement to be highlighted. The second section will analyze the recommendations and how they have evolved over time. This analysis is being completed to provide a firm understanding of the target-populations which is vital for the discussion on the research being used to substantiate the recommendations.

PROCESS OF MAKING RECOMMENDATIONS

WHO Process

The World Health Organization and the Centers for Disease Control and Prevention use similar processes for creating the target-population recommendations for influenza vaccinations. These processes are meant to be evidence-based and transparent. This section will discuss the process used by each group, then compare the two processes to each other and to the general policymaking framework discussed in chapter two.

The World Health Organization relies upon the Strategic Advisory Group of Experts (SAGE) to assist in making vaccine recommendations. SAGE's role is to advise the Director-General on progress towards achievement of goals, collaboration of the Global Vaccine Action Plan, immunization program responses to current public health

priorities, and the overall adequacy of the WHO's strategic plan.[304] Recommendations are expected to be evidence-based, transparent, reliable, and have minimal conflicts of interest.[305] As an advisory board, SAGE has "no executive or regulation function. Its sole role is to provide advice and recommendations to the Director-General of WHO."[306] Importantly, WHO itself lacks legislative and executive authority within member countries. WHO recommendations are not binding, although they are highly influential in drafting country level policies.

Members of SAGE are appointed for three-year, renewable terms. Members are required to have an understanding of vaccination and immunization issues at the global level, outstanding records of achievement and personal credibility within their field, and experience in high-level advisory committees.[307] In addition to excellent interpersonal communication skills, members must possess the ability to evaluate complex issues at a high level along with a command of English, and a broad range of expertise and interests.[308]

SAGE meets biannually at WHO Headquarters in Geneva for three days, normally in April and November. Working groups meet via teleconference and in person as required to fulfill their Terms of Reference.[309] During the biannual meeting, working groups (WGs) present their findings and preliminary recommendations. WGs are

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[304] World Health Organization. "Strategic Advisory Group of Experts (SAGE) Terms of Reference," last modified February 9, 2016. http://www.who.int/immunization/sage/Full_SAGE_TORs.pdf?ua=1.

[305] Ibid.

[306] Ibid.

[307] Ibid.

[308] Ibid.

[309] Terms of Reference are used by the WHO to delineate the scope of work required for a particular role.

established to increase the effectiveness of SAGE deliberations when issues cannot be adequately addressed by standing committees.[310] Consisting of up to twelve members, WGs operate under specific terms of reference that must be defined within thirty days of the group's establishment.[311] Members include at least one member of SAGE, who acts as the Chair and include other subject matter experts as required.[312] The chair must have at least one year of experience as a voting member prior to being appointment as chair. Members are nominated through a public call on the SAGE website and replacements can be made as need from the original list of candidates without having to reopen the call. WGs meet via teleconference at least monthly and generally have an in-person meeting a minimum of one month prior to the SAGE meeting where the findings and preliminary recommendations of the group will be presented.

After the WG is convened, the group defines the questions needed to inform the recommendations. This is often done in Population/Intervention/Comparator/Outcome (PICO)format which is a well-accepted methodology for systematic reviews.[313] If a systematic review on the topic exists, the WG will update the review to provide the evidence base and foundation for the question at hand. Otherwise, they will complete or commission the creation of one. Once the review is complete, the evidence will be reviewed and evaluated per the Grading of Recommendation Assessment Development and Evaluation (GRADE) methodology, which has been required since 2007, with

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[310] World Health Organization. "Purpose, Structure and Functioning of the Strategic Advisory Group of Experts on Immunization (SAGE) Working Groups." Accessed February 24, 2016. http://www.who.int/immunization/sage/SAGE_Working_Groups_general_information.pdf?ua=1.

[311] Ibid.

[312] Ibid.

[313] P. Duclos, et al., "Developing Evidence-Based Immunization Recommendations and GRADE." *Vaccine* 31, no. 1 (2012): 12–19. doi:10.1016/j.vaccine.2012.02.041.

special attention to the risk of bias in the studies.[314] Discussion and deliberation of recommendations begin once the evidence is reviewed with the WG eventually coming to a consensus that is presented to SAGE for further discussion. WGs are not authorized to communicate their findings or recommendations directly to the Director-General nor are their meeting minutes made public. WG reports are published as background papers for the SAGE meetings, and the publication of the reports in peer-reviewed journals is encouraged. Once WGs findings and recommendations are presented to SAGE for discussion the final recommendations are drafted and then provided to the WHO Director-General for action. SAGE recommendations are also published on the WHO website, in the *Weekly Epidemiological Record,* and in peer-reviewed journals.

CDC Process

The Centers for Disease Control and Prevention is the leading public health agency in the United States with the mission to "fight disease and support communities and citizens to do the same."[315] One of the ways the CDC supports this mission the promulgation of vaccination schedules and recommendations. The Advisory Committee on Immunization Practices (ACIP) is an advisory board within the CDC specializing in immunizations. The ACIP's role is to:

> assist states and their political subdivisions in the prevention and control of communicable diseases; to advise the states on matters relating to the preservation and improvement of the public's health' and to make grants to states and, in consultation with the state health authorities, to agencies

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[314] World Health Organization, "Guidance for the Development of Evidence-Based Vaccine-Related Recommendations,"2015. http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf.

[315] Centers for Disease Control and Prevention, "Mission, Role and Pledge | About | CDC." About CDC 24-7. Accessed March 23, 2016. http://www.cdc.gov/about/organization/mission.htm.

> and political subdivisions of states to assist in meeting the costs of communicable disease control programs.[316]

The ACIP is responsible for providing advice and guidance on the selection of vaccines for control of vaccine-preventable diseases, specifically, the populations to be vaccinated and type of preparation to be used, the route, dose, and frequency of administration, as well as contraindications and precautions.[317] Like SAGE, ACIP is an advisory group which "has no executive or regulatory function. Its sole role is to provide advice and recommendations to the Directors of CDC."[318]

ACIP is made up of fifteen voting members, including the chair, eight nonvoting ex-officio members, and non-voting liaison representatives from various healthcare and professional societies.[319] Voting members are selected by the Secretary of the Department of Health and Human Services from authorities in fields of immunization and public health having expertise in vaccine use, clinical/lab vaccine expertise and expertise in assessment of vaccine efficacy and safety along with a member knowledgeable in community/consumer perspectives.[320] Members can serve for overlapping terms of up to four years, but terms of more than two years are contingent upon approval by the committee. The Chair is appointed for a three-year term and must have at least one-year experience as a voting member prior to appointment. Nominations and applications can be made directly to the Secretary of the Department of Health and Human Services.

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[316] Centers for Disease Control and Prevention. "ACIP Charter".

[317] Ibid.

[318] Centers for Disease Control and Prevention. "Advisory Committee on Immunization Practices: Application for Membership." Accessed February 24, 2016. http://www.cdc.gov/vaccines/acip/committee/downloads/nominations.pdf.

[319] Ibid.

[320] Ibid.

ACIP meetings are held three times per year, February, June, and October, at the Global Communication Center in Atlanta, Georgia while working groups meet via teleconference monthly. ACIP has four standing WGs: adult immunizations, influenza vaccines, general recommendations, and harmonized schedule for children and adolescents.[321] Other WGs are created on as as-needed basis. The purpose of the ACIP WGs, like the SAGE WGs, is to conduct in-depth data reviews and develop preliminary recommendations for consideration by the full committee. Each WG includes two ACIP members and a CDC subject matter expert; other members are invited as their expertise is required. Vaccine manufacturers are occasionally invited to present study findings but cannot be WG members.[322] WG chairs present findings and preliminary recommendations for consideration of the committee, which deliberates and puts recommendations to a vote. A quorum of at least eight eligible committee members or ex-officio members is required for a vote- lack of a quorum is rare.[323] Under the Federal Advisory Committee Act of 1972, all ACIP meetings must be announced in the *Federal Register* at least fifteen days prior to the meeting dates to give members of the public an opportunity to attend the meeting to speak or submit written statements. Meetings minutes and recommendations are posted on the ACIP website within ninety days of the meeting; slides are available within two weeks.[324] Since July 2009, meetings have been broadcast and saved online.[325] Final ACIP recommendations are published in *Morbidity*

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[321] Jean Clare Smith, "The Structure, Role, and Procedures of the U.S. Advisory Committee on Immunization Practices (ACIP)," *Vaccine* 28 Suppl 1 (April 19, 2010): A68–75, A72. doi:10.1016/j.vaccine.2010.02.037.

[322] Ibid., A72.

[323] Ibid., A73.

[324] Ibid., A70.

[325] Ibid., A74.

and Mortality Weekly Report following CDC approval.[326] Although ACIP lacks legislative authority, recommendations are almost always accepted by the CDC. The exception to ACIP recommendations being accepted by the CDC Director occurred in 2003 when ACIP recommended using the smallpox vaccine in a pre-event vaccination program, and the CDC Director rejected this recommendation.[327] When ACIP recommendations are accepted, they become national policy. As policy, insurers base reimbursement guidelines for vaccines and public health agencies base outreach activities on these recommendations.[328]

Comparisons

The WHO and CDC use similar processes to make target-population recommendations for influenza vaccines. The main differences between the processes are the audiences for the recommendations, the agency's legislative authority, and the frequency of recommendations. The WHO recommendations are meant for national level policymakers while the CDC recommendations are intended for U.S. insurers, state/local public health officials, and the public. The CDC has legislative authority to determine vaccination schedules. The CDC also makes recommendations annually whereas the WHO has only issued statements regarding the target-population recommendations three times.

WHO and CDC communicate their recommendations in a similar fashion, via web publication, official agency publications, and peer-reviewed journals. The

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[326] Ibid., A70.
[327] Ibid., A73.
[328] Ibid., A71.

communication of the recommendations is one of the areas which needs improvement. While the target-population recommendations are freely available via the web, they are not accessible to the average person due to the way they are written. The target-population recommendations are written by highly educated scientific experts and read as such. They are full of scientific jargon and complex language; I would estimate that they are written at least at a college level; the average person reads at less than an eighth grade level.[329] The 2005 target-population recommendations from the CDC were forty-six printed pages and included 349 sources. As a researcher, I found this to be a fabulous source of information. However, as the primary caregiver for a disabled person, the information was overwhelming. Without the benefit of a post-graduate education, I would not have been able to determine if the influenza vaccine was appropriate for my sixty-one-year-old disabled mother with chronic cardiopulmonary disorders.

The WHO and CDC processes are more streamlined than the general policymaking process outlined in chapter two. Like the general policymaking process, SAGE and ACIP both require a clear goal and problem to be defined, involve the evaluation of potential solutions and determination of the right solution. The flow chart below illustrates the processes used by during the general policymaking framework and SAGE/ACIP:

[329] Kutner, M, Greenberg, E, Jin, Y, and Paulsen, C, (2006) The Health Literacy of America's Adults: *Results From the 2003 National Assessment of Adult Literacy* (NCES 2006-483). U.S. Department of Education, Washington, DC, National Center for Education Statistics.

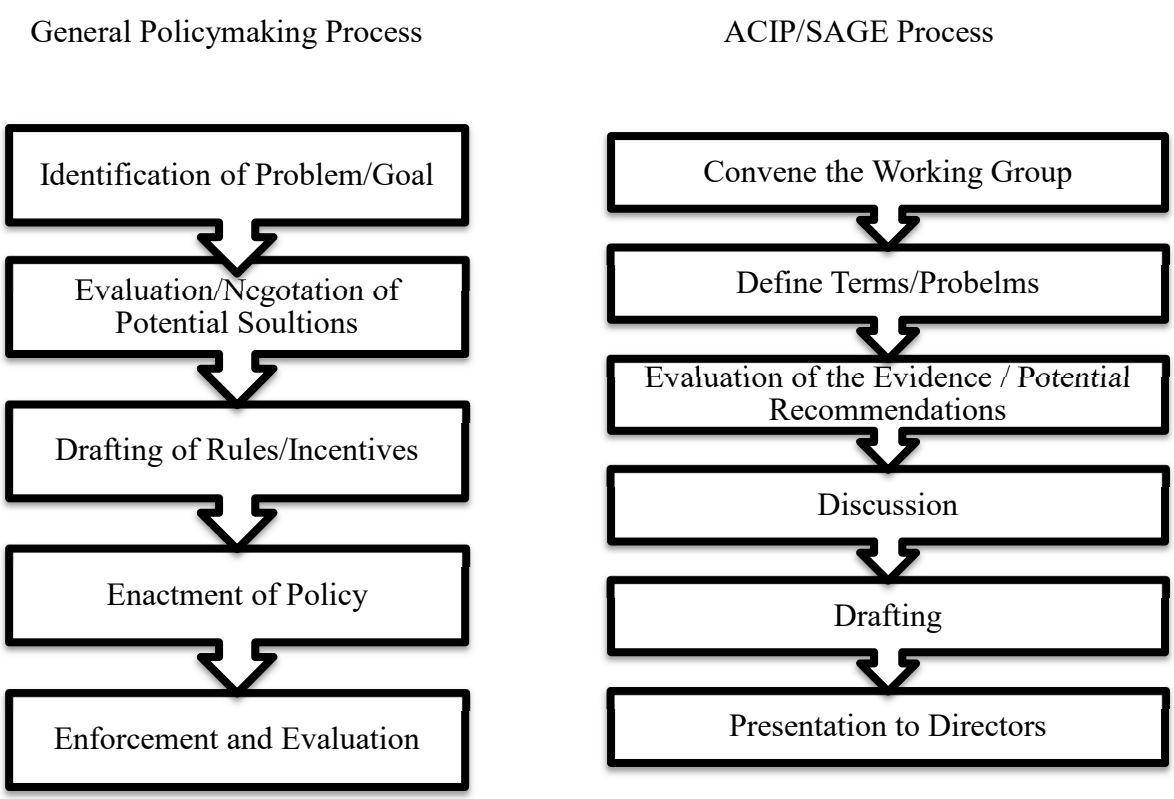

FIGURE 4: COMPARISON OF GENERAL POLICYMAKING AND CDC/WHO PROCESSES

While it may appear that the SAGE/ACIP process is more complicated than the general policymaking process, the process is streamlined to allow for a more thorough review in a shorter amount of time. When the terms and problems are being defined by the WGs, they are finely articulated versus actually being defined as would be required in the general policymaking process. As advisory boards, the missions of SAGE and ACIP are narrow and therefore, the issues that they are able to address make defining the issues simpler. SAGE and ACIP are also less politically motivated than other policymakers because they are not facing reelection nor do they have to contend with other legislative initiatives or goals. The members of SAGE and ACIP are there to fulfill professional duties; while conflicts of interest may exist both groups have robust plans in place to manage and mitigate conflicts of interest. While the target-population recommendation

process is arguably more evidence-based than the general policymaking process and avoids some of the challenges of evidence-based policymaking discussed in chapter two, the question remains if the evidence base for the recommendations is appropriate. The chapter four will analyze the types of research used in making the target-population recommendations and how that research is evaluated.

ANALYSIS AND COMPARISON OF WHO AND CDC RECOMMENDATIONS

Target-population recommendations are determined using a process that strives for transparency and quality. The target-populations attempt to identify the groups at highest risk for contracting influenza and suffering from severe illness. These recommendations guide allocation and promote public health. Target-population recommendations are published yearly by the CDC and were last updated in 2012 by the WHO. This section will analyze the recommendations and how they have changed over time. A comparison of the recommendation of the WHO and CDC will also be completed along with a discussion of the evidence needed to support the recommendations.

WHO Recommendations

The WHO publishes positions papers on vaccines that target diseases with an international health impact.[330] These position papers provide a summary of the epidemiological information and the current WHO position on the global use of the vaccines. The intended audience for the position papers is national public health officials

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[330] World Health Organization, "Influenza Vaccines WHO Position Paper," *Weekly Epidemiological Record* no. 28 (July 12, 2002);230-239, 230.; World Health Organization, "Influenza Vaccines WHO Position Paper," Weekly Epidemiological Record 80, no. 33 (August 19, 2005): 277-88., 279.; World Health Organization, "Vaccines against Influenza WHO Position Paper - November 2012," *Weekly Epidemiology Record* 87, no. 47 (November 23, 2012): 461-76., 461.

and vaccine program managers.[331] The World Health Organization began publishing policy positions on influenza vaccinations as a part of the Global Agenda on Influenza.[332] The Global Agenda on Influenza was adopted in 2002 to outline activities "critical to mobilizing action to reduce morbidity and mortality due to annual influenza epidemics and prepare for the next influenza pandemic."[333] The 2002 position statement on influenza vaccines was meant to be an interim statement, pending further development by the Global Influenza Program, but was not updated until 2005.[334] The WHO's position on influenza vaccines was last updated in 2012.[335]

The WHO recommended in 2002 that all individuals be vaccinated when major influenza outbreaks are expected but also understood that limited health budgets and supplies required distribution restrictions to groups at particular risk.[336] The following populations were recommended in priority order:

> 1. Residents of long-term care facilities for the elderly and disabled
> 2. Elderly non-institutionalized persons who suffer from chronic conditions such as pulmonary or cardiovascular illness, metabolic diseases including diabetes mellitus and renal dysfunction, and various types of immunosuppression including persons with AIDS and transplant recipients.
> 3. All adults and children over 6 months of age who suffer from any of the conditions mentioned above.

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[331] Ibid. Any vaccine recommended by the WHO must meet six general criteria: (1) meet the current WHO quality requirements; (2) be safe and have a significant impact on the actual disease in all target-populations; (3) be easily adapted to schedules and times of the national childhood immunization programs, if intended for infants or young children; (4) not interfere significantly with the immune response to other vaccines given simultaneously; (5) be formulated to meet common technical requirements in terms of refrigeration and storage; and (6) be appropriately priced for different markets

[332] World Health Organization, "Adoption of Global Agenda on Influenza-part II" *Weekly Epidemiological* Record 77, no. 23 (June 7, 2002): 191-196, 191.

[333] World Health Organization, "Adoption of Global Agenda on Influenza-part II" 191.

[334] World Health Organization, "Influenza Vaccines WHO Position Paper 2002" 230.

[335] World Health Organization, "Vaccines against Influenza WHO Position Paper - November 2012"

[336] World Health Organization, "Influenza Vaccines WHO Position Paper 2002" 238.

4. Individuals who are above a nationally defined age limit irrespective of other risk factors. (Most countries use 65 years.)
5. Other groups defined on the basis of national data.
6. Health care workers in regular, frequent contact with high-risk persons.
7. Household contacts of high-risk persons.[337]

These groups represent the then-current assumptions of who was at most risk of severe outcomes and premature death from influenza infections and resulting complications. While it is noted within the text that the highest rates of morbidity and mortality occur in people over sixty-five and with chronic ailments specific references are not provided.[338] Pregnant women were not included as a part of the target-populations. Instead, pregnant women in their second or third trimester were recommended to consult their health care provider regarding the need for an influenza vaccination.[339] Importantly, the recommendations also gave needed flexibility and deference to national needs based upon country-level data.

The 2005 position paper retained priority designations for at-risk populations but reorganized and condensed the groups. The recommendations only applied to the trivalent, inactivated vaccines, although the live, attenuated influenza vaccine was available in the United States and Russia as of 2003.[340] The 2005 target-population recommendations, again listed in priority order, were:

1. Residents of institutions for elderly people and the disabled.
2. Elderly, non-institutionalized individuals with chronic heart or lung diseases, metabolic or renal disease, or immunodeficiencies.
3. All individuals >6 months of age with any of the conditions listed above.

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[337] World Health Organization, "Influenza Vaccines WHO Position Paper 2002" 238-9.
[338] World Health Organization, "Influenza Vaccines WHO Position Paper 2002" 232.
[339] World Health Organization, "Influenza Vaccines WHO Position Paper 2002" 239.
[340] World Health Organization, "Influenza Vaccines WHO Position Paper 2005" 287.

4. Elderly individuals above a nationally defined age limit, irrespective of other risk factors.
5. Other groups defined on the basis of national data and capacities, such as contacts of high-risk people, pregnant women, health-care workers and others with key functions in society, as well as children 6–23 months of age.[341]

The 2005 position paper combined household contacts of risk groups, pregnant women, healthcare workers and groups based on national data into one category.[342] The vaccination of pregnant women was recommended unequivocally, while it was recommended in 2002 that pregnant women discuss the need for the vaccination with their healthcare provider.[343] This change indicates that additional research had become available, but no specific citations were provided within the text of the recommendations. Background papers from the 2005 SAGE meetings are not readily accessible online.[344] The reorganization of the groups allowed WHO to continue to prioritize those considered most at risk, institutionalized, those with chronic conditions, and the elderly while giving deference to the country-level risk and preference based upon needs and capacities of the area.

The 2012 position paper made a massive departure from the two previous position statements by removing priority from all populations. The following risk groups were recommended "in no particular order of priority:"[345]

1. Pregnant women,
2. children aged 6-59 months,

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[341] World Health Organization, "Influenza Vaccines WHO Position Paper 2005" 280.
[342] World Health Organization, "Influenza Vaccines WHO Position Paper 2005" 280.
[343] World Health Organization, "Influenza Vaccines WHO Position Paper 2005 286
[344] Background papers are commissioned by SAGE and used to base discussion and therefore decisions upon. Information from the 2012 meeting is readily available but the 2002 and 2005 meeting information is not.
[345] World Health Organization, "Vaccines against Influenza WHO Position Paper - November 2012" 474.

3. the elderly,
4. individuals with specific chronic medical conditions,
5. and health care workers

The WHO recommended that pregnant women receive priority *only when the country is initiating or expanding influenza programs*.[346] Existing programs were encouraged to continue efforts in increasing influenza vaccination rates for all risk groups. The WHO determined that these groups were at "increased risk of exposure to influenza virus as well as those at particular risk of developing severe disease." [347] The specific rationale for the populations are summarized in the table below:

Population	**Rationale**
Pregnant Women	Increase risk of severe disease and death; infection also leads to complications such as stillbirth, neonatal death, preterm delivery and decreased birthweight. Pregnant women were 7.2 times more likely to be hospitalized during the 2009 pandemic (in NYC)
Children	Under five, particularly under 2 have a high burden of influenza resulting in an estimate of 90 million cases of seasonal influenza and 20 million acute lower respiratory infections in 2008. In the US, rates of hospitalization in preschoolers are comparable to the elderly. Children are also very effective vectors.
Elderly	Influenza is a known contributor to mortality. Between 1976-2007, 90% of influenza deaths in the USA occurred in those over 65. In China, 86% of influenza-associated deaths in 2003-2008 occurred in

[346] World Health Organization, "Vaccines against Influenza WHO Position Paper - November 2012" 474.

[347] World Health Organization, "Vaccines against Influenza WHO Position Paper – November" 463.

	those over 65.
Individuals with specific chronic health conditions	Severe illness from influenza virus infection continues to be a concern for those with specific chronic conditions, but the identification of the appropriate target conditions will vary on a country level
Health Care Workers	Health care workers contribute to hospital-based transmission of influenza to patients.

Table 1: Summary of WHO Rationale for 2012 Target-Populations Table Source: World Health Organization, "Vaccines against Influenza WHO Position Paper - November 2012," *Weekly Epidemiology Record* 87, no. 47 (November 23, 2012): 461-76

The 2012 position statement on influenza vaccines was the first time that citations were used in the text of the recommendations. This change corresponded with the WHO adoption of the GRADE methodology in 2007. What is unexplained is the removal of the priority designation from the populations. The WHO gave the overall rationale for the changes as:

> important developments in this field such as new data on the epidemiology of influenza in developing and tropical countries, new evidence on the consequences of influenza virus infection in pregnant women, and information on pandemic as well as seasonal manifestations of the A(H1N1)pdm09 strain of influenza.[348]

The 2004/2005 influenza vaccine shortage and the 2009 H1N1 pandemic undoubtedly had an impact on the 2012 recommendations. Additionally, the Decade of Vaccines was launched in collaboration with the Bill and Melinda Gates Foundation, the WHO, UNICEF, and the NIH in December 2010 with the goal of increasing access to vaccines in low and middle/low-income countries.[349] Removing priority language from the

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[348] World Health Organization, "Vaccines against Influenza WHO Position Paper - November 2012 461.

[349] Magdalena Robert, "Global Health Leaders Launch Decade of Vaccines Collaboration | Bill & Melinda Gates Foundation," Press Release, 2010. http://www.gatesfoundation.org/Media-Center/Press-Releases/2010/12/Global-Health-Leaders-Launch-Decade-of-Vaccines-Collaboration.

recommendations brought the recommendations more in-line with the objective of the Decade of Vaccines to equitably extend the benefits of immunizations to all people.[350] The WHO recommendation can be seen as increasing access by removing priority designations for specific groups and instead focusing on general risk groups and encouraging countries to make policy based on national level data. Removing the priority designation also promotes influenza vaccination for all populations, where the priority designations limit the access to those within the designation by implying that those populations are the ones that truly benefit from the vaccination and thus conversely implying that vaccinating other populations is not necessary.

CDC Recommendations

Seasonal influenza vaccinations have been recommended in the United States since 1960.[351] This information is published in *Morbidity and Mortality Weekly,* and the ACIP meetings are open to the public and available for online viewing. In order to provide a more direct comparison to the WHO recommendations only, the 2002-2012 CDC recommendation will be analyzed in this section.

CDC's recommendations steadily expanded between 2002 and 2010 when the ACIP began recommending all individuals without a contraindication receive the seasonal influenza vaccine. As of 2010 target-populations were designated only in the

[350] The Decade of Vaccines has six strategic objectives which can be found at: http://www.who.int/immunization/global_vaccine_action_plan/GVAP_Strategic_Objective_1-6.pdf?ua=1

[351] Leroy E. Burney. "Influenza Immunization: Statement." *Public Health Reports* 75, no. 10 (October 1960): 944.

event of a vaccine shortage.[352] CDC divides its target-population recommendations into two categories, those who are at increased risk for complications and those who can transmit influenza to high-risk populations.[353] The 2002 and 2003 influenza vaccination target-population recommendation were[354]:

Patients at High Risk for Complications:

1. persons aged >65 years;
2. residents of nursing homes and long-term care facilities who have chronic medical conditions;
3. adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma;
4. adults and children who have required regular medical follow-up or were hospitalized during the preceding year due to chronic diseases;
5. children and adolescents (aged 6 months--18 years) who are receiving long-term aspirin therapy (increased risk of Reye syndrome
6. women in the second or third trimester of pregnancy[355]

Persons Who Can Transmit to at Risk Populations

1. physicians, nurses, and other personnel in both hospital and outpatient-care settings, including emergency medical services personnel
2. employees of nursing homes and long-term care facilities who have contact with patients or residents;
3. employees of assisted living and other residences for persons in groups at high risk;
4. persons who provide home care to persons in groups at high risk; and
5. Household contacts (including children) of persons in groups at risk.

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[352] Anthony E. Fiore, et al. "Prevention and Control of Influenza with Vaccines." *Morbidity and Mortality Weekly* 59RR08(August 6, 2010): 1–62. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5908a1.htm.

[353] Carolyn B. Bridges, et al. "Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP)." *Morbidity and Mortality Weekly* 52, RR03 (April 12, 2002): 1–31. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5103a1.htm.; Carolyn Bridges, et al. "Prevention and Control of Influenza." *Morbidity and Mortality Weekly* 52 RR08 (April 23, 2003): 1–36. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5208a1.htm.

[354] Ibid.

[355] Ibid.

In 2004, the CDC expanded the child immunization recommendation to include healthy children aged 6 to 23 months, and close contacts of children aged 0 to 23 months.[356] This expansion is based on five studies that show that young children experience increased rates of hospitalization.[357] Children under the six months of age have the greatest risk for influenza-related complications, but the vaccine is not FDA approved for this population- thus, protection depends on vaccinating their household contacts.

Two populations were expanded with the 2005 recommendations, those with compromised respiratory systems and healthcare workers.[358] The category of chronic pulmonary disease was expanded to include any person with a condition that compromises respiratory function or increases the risk of aspiration as opposed to chronic pulmonary disorders.[359] CDC recommended that all health-care workers be vaccinated, instead of specifying the work areas. This was based on research showing that health-care worker vaccination is associated with decreased deaths in nursing home patients and reduction in lost work days for employees.[360] Additionally, the live, attenuated influenza vaccine was approved for healthy non-pregnant persons aged 5 to 49 in 2005.[361]

The healthy children category was again expanded in 2006 when the ACIP recommended that healthy children aged 24 to 59 months, their household contacts, and

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[356] Scott A. Harper, et al. "Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP)." *Morbidity and Mortality Weekly* 53 RR06 (May 28, 2004): 1–40. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5306a1.htm.

[357] Ibid. These studies included observational and RCT methods.

[358] Scott A. Harper, et al. "Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP)." *Morbidity and Mortality Weekly* 54 Early Release (July 13,2005): 1–40. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr54e713a1.htm.

[359] Ibid.

[360] Ibid.

[361] Ibid.

out-of-home caregivers be vaccinated.[362] This recommendation was based on population-based surveillance between 2000 and 2004 which revealed that treating physicians were failing to diagnose influenza in young children despite the clinical presentation of illness.[363] This change highlights the use of evidence-based recommendations. When the research highlighted a problem, in this case, the under-diagnosis of influenza, policy was created to address the problem. Following this expansion, all children age six to 59 months were recommended to receive the seasonal influenza vaccine.[364] In 2008, the ACIP further expanded the child recommendation to include the annual vaccination of children between five and eighteen years of age.[365] The expansion was based on accumulated evidence regarding safety and efficacy in healthy children, combined with the continued high burden of influenza in children and the need for a more simplified recommendation to improve vaccine coverage levels.[366]

The final expansion of the target groups occurred in 2010 when ACIP recommended that all persons over 6 months of age without contraindications receive the influenza vaccine.[367] At the time of this expansion, the only group that did not have a recommendation for a seasonal influenza vaccine were healthy, non-pregnant adults aged 18-40 who also did not have an occupational risk and were not close contacts with at-risk

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[362] Nicole M. Smith, et al. "Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP)." *Morbidity and Mortality Weekly* 55 RR10 (July 28, 2006): 1–42. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5510a1.htm.

[363] Katherine A. Poehling, et al. "The Underrecognized Burden of Influenza in Young Children." *The New England Journal of Medicine* 355, no. 1 (July 6, 2006): 31–40. doi:10.1056/NEJMoa054869.

[364] Ibid.

[365] Anthony E. Fiore, et al. "Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008." *Morbidity and Mortality Weekly* 57 Early Release (July 17, 2008): 1–60. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr57e717a1.htm.

[366] Ibid.

[367] Anthony E. Fiore, et al. "Prevention and Control of Influenza with Vaccines." *Morbidity and Mortality Weekly* 59, no. (RR08) (August 6, 2010): 1–62. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5908a1.htm.

populations or children.[368] Prior to this final expansion, 85% of the population was included in the target groups; the "universal vaccination recommendation for all persons aged ≥6 months eliminates the need to determine whether each person has an indication for vaccination and emphasizes the importance of preventing influenza among person of all ages."

ACIP continues to recommend target-populations in the event of a vaccine shortage:

1. all children aged 6 months--4 years (59 months);
2. all persons aged ≥50 years;
3. adults and children who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurological, blood, or metabolic disorders;
4. persons who have immunosuppression;
5. women who are or will be pregnant during the influenza season;
6. children and adolescents (aged 6 months--18 years) who are receiving long-term aspirin therapy and who might be at risk for experiencing Reye syndrome after influenza virus infection;
7. residents of nursing homes and other long-term--care facilities;
8. American Indians/Alaska Natives;
9. persons who are morbidly obese (BMI ≥40);
10. health care personnel;
11. household contacts and caregivers of children aged <5 years and adults aged ≥50 years, with particular emphasis on vaccinating contacts of children aged <6 months; and
12. household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza.[369]

American Indians/Alaska Natives and the morbidly obese are additions to the target groups after observational studies during the 2009 pandemic indicated that these groups might be at a higher risk for complications including death.[370] Having the universal recommendation in combination with the target-population recommendations in the event

[368] Ibid.
[369] Ibid.
[370] Ibid.

of a vaccine shortage allows for the CDC to promote yearly influenza vaccination for all populations.

Comparisons

The recommendations of the WHO and the CDC highlight the differences and similarities between the two advisory boards. WHO's recommendations reflect the desire to reflect the mission to reduce severe outcomes and premature death in the most at-risk populations. The CDC recommendation reflects the resources of an industrialized nation to provide routine immunizations for the majority of its population while still being attuned to potential vaccine shortages. Both groups strive to increase vaccine coverage and reduce the overall burden of infection.

The main difference in the language used between the two sets of recommendations is the absence of the term priority from the CDC recommendations. While the WHO explicitly gave priority to certain groups in 2002 and 2005, CDC has consistently used the phrase "focus efforts" in regards to providing vaccine to target groups. The WHO altering the language from priority to risk groups may have been in response, at least in part, to the CDC's recommendation that all populations receive the seasonal influenza vaccine with specific target-populations in the event of a vaccine shortage. Alternatively, this could simply be a stylistic change meant to encourage nations to make policy based on country level data.

CDC has consistently recommended a larger number of populations to receive the influenza vaccine than the WHO. This is reflective of the fact that the WHO recommendations are meant to be customized to a nation's risk and resource level. The United States is also a high-income nation with a plethora of resources at its disposal.

In reviewing the target-population recommendations, the question becomes what evidence supported the changes in the recommendations. Having the entire population vaccinated against influenza would reduce the socioeconomic burden of infection, and more importantly save lives. Still, it is unlikely that all persons without a contraindication would receive an influenza vaccination even if it were available. I would argue that having a robust evidence base that was well communicated to policymakers and the public would increase vaccination rates.

Conclusion

This chapter sought to provide an overview of the processes used to create the target-population recommendations for the influenza vaccine and the evolution of the recommendations over time. This overview was completed for three reasons. First, to provide a comparison between the recommendation and processes used by WHO and CDC. Second, to provide a historical review of the target-population recommendations. Finally, to provide the foundation for the types of evidence required to support to recommendations. This evaluation is limited by the fact that the WHO has only provided three target-population recommendations. It is also difficult to compare the work of the CDC and WHO given the stark differences in resources available for the two agencies. The WHO must make policies which can be adopted across socioeconomic conditions whereas the CDC makes policy for a resource rich nation. This accounts for the difference in the target-populations, the WHO recommends seven, the CDC current recommends seventeen.

The target-population recommendations for influenza vaccination are created by the WHO and CDC using a process that improves upon the general policymaking process

outlined in chapter two. The recommendations have evolved over time although the changes have not been well cited by the WHO. Chapter four will examine the types research used to determine the target-population recommendations and how the quality of research is evaluated.

Chapter Four: Research Evaluation Methodologies

Influenza vaccine target-population recommendations impact the management of seasonal and pandemic influenza by determining priority allocation of the vaccine in the event of a shortage. A downside of the target-population recommendations is the misconception that, due to their increased risk, only the target-populations should be vaccinated against the influenza virus. This misconception requires that the target-population recommendations be accurate but also work to improve all vaccination rates when vaccine supplies are available.

Researchers and policymakers share a joint obligation to the public to ensure that target-population recommendations are based on high-quality research. High-quality clinical research is required for the production of evidence-based health policy, as documented in chapters two and three. Research requires evaluation for three reasons. First, evaluation is a part of the peer-review process. Evaluation allows for critique and improvement which is vital to the scientific process. Evaluation also helps discover errors and biases that may have otherwise gone unnoticed. While researchers rarely intentionally produce misleading or inaccurate results mistakes occur, and evaluation allows those mistakes to be uncovered. Finally, evaluation provides an additional level of protection to the public who are impacted by the policies created from the research. Research evaluation methodologies have been developed to allow for the systematic, transparent appraisal of studies to ensure that research used in recommendations has been planned, completed and reported in an acceptable and standardized manner.

This chapter explores if research evaluation methodologies can accurately and fairly appraise the evidence base for influenza vaccine target-population

recommendations. Three aims will be met in this chapter. Aim one is to determine the types of research available and used in target-population recommendations. Aim two is to discuss the research evaluation methodologies and evaluate their application to the target-population recommendations. Aim three is to recommend potential changes to the evaluation methodologies. The chapter will be completed in two sections. The first section will address the types of research generally and specifically used in the target-population recommendations. The second section will shift the discussion to the research evaluation methodologies available and evaluate their application to the target-population recommendation evidence base.

TYPES OF RESEARCH

Research is defined as a "systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge."[371] There are three main types of medical research: basic, clinical, and epidemiological. While influenza research occurs in all areas, I will focus on clinical and epidemiological research due to its greater impact on target-population recommendations and policy making as a whole.[372] Most influenza research is applied research- meaning the research is working towards a solution of a known problem, such as preventing

[371] "Human Subjects Research" 45 C.F.R. 46.106(d)

[372] See Bernd Röhrig, Jean-Baptist du Prel, Daniel Wachtlin, and Maria Blettner. "Types of Study in Medical Research: Part 3 of a Series on Evaluation of Scientific Publications." *Deutsches Ärzteblatt International 106*, no. 15 (April 2009): 262–68. doi:10.3238/arztebl.2009.0262 Basic research, also known as bench science or experimental research, includes animal experiments, cell studies, biochemical, genetic and physiological investigations, and studies on the properties of drugs and material. Also includes the development and improvement of analytical and biometric procedures.

influenza infections or severe outcomes.[373] Research design follows a three step process. First, the problem must be identified, followed by the background of the problem being given.[374] The objectives and testable hypothesis to achieve that objective are then outlined.[375] The methodology for testing the hypothesis, including the populations, type of study, procedures, and data collection, are then described and justified.[376] The required resources for the project, the justification for the project as a whole and plans for dissemination are also given.[377] As discussed in chapter two, policymaking follows a similar process of problem identification, background research, goal setting, crafting a solution, and dissemination. Like policymakers, researchers face the challenge of ensuring that their methods are suitable for the objectives. Like policymakers, researchers face external pressures which can inadvertently impact their work, illustrating the need for balanced, external evaluation methods.

Clinical research evaluates the impact of interventions in the human population through either interventional or observational methods. All clinical research requires informed consent, or an exemption, and are expected to meet Good Clinical Practices and ICH Guidelines.[378] Interventional trials study the impact of the therapy in the study population with the randomized controlled trial (RCTs) being one of the most

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[373] WHO Regional Office for the Western Pacific. Health Research Methodology: A Guide for Training in Research Methods. 2nd ed. Albany, NY: WHO Pacific Regional Office, 2001., 2.

[374] WHO Regional Office for the Western Pacific. Health Research Methodology 8-9.

[375] Ibid.

[376] Ibid.

[377] Ibid.

[378] Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording and reporting research involving human subjects. ICH Guidelines are the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. See ich.org

common.[379] RCTs can be done for a variety of purposes including assessment of safety, effectiveness, or efficacy, and are required to support New Drug Applications to the Food and Drug Administration.[380]

Observational studies compare the impacts of the intervention within the study population based on the medical diagnosis and the patient's desire for treatment.[381] These studies allow researchers to analyze how the influenza virus and vaccine behave under various naturally occurring conditions, bolstering the knowledge base for real-world applications. Observational studies are not blinded but can be controlled through recruitment and case selection. Another key difference between observational and interventional clinical studies is that observational studies can be done retrospectively; meaning that the subject is 'enrolled,' and the study completed after the patient has completed the therapy. Observational studies follow a course of therapy similar to a clinical trial in a head-to-head comparison or can be used to determine how other health

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[379] Röhrig, Baptist du Prel, Wachtlin and Blettner. "Types of Study in Medical Research" 263.

[380] U.S. Department of Health and Human Services, Food and Drug Administration. "Guidance for Industry: Providing Clinical Evidence on Effectiveness for Human Drugs and Biological Products." May 1998. Accessed May 30, 2016. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf Interventional trials are completed in four phases. In Phase I trials, researchers evaluated the treatment for safety in the human population and identified side effects for the safe dosage range. Phase I trials have the lowest number of participants and are often completed using healthy subjects. Effectiveness begins to be evaluated in Phase 2 where the intervention is given to a larger group of people. Safety evaluation continues in Phase 2 studies. Phase 3 studies are the largest and can include thousands of patients in multiple locations. The purpose of Phase 3 trials is to confirm the treatment's effectiveness, monitor side effects, provide comparisons to common treatments, and collect information that will be required to use the treatment safely. Once the FDA approves the treatment, Phase 4 trials (also known as post-marketing trials) can begin which provide additional information on risks, benefits, and best use.

[381] Röhrig, Baptist du Prel, Wachtlin and Blettner. "Types of Study in Medical Research" 265.

factors impact disease progression (prognosis studies) and how diagnoses are made.[382] Observational research also includes secondary data analysis and case reports.[383]

Epidemiological studies seek to determine the distribution and changes in diseases over time as well as the causes for those changes.[384] Like clinical research, epidemiological research can be divided into interventional and observational studies. Interventional epidemiological studies study the impact of a particular change on a disease over time. An example of an interventional epidemiological study in influenza would be if the impact of the influenza vaccine on acute respiratory infection rates over a set amount of time in a given area.

Observational epidemiological studies are completed to show disease progression over time. In cohort studies, also called follow-up and longitudinal studies, researchers obtain information at the start of the study, follow the participants over a set period of time, then assess the occurrence of outcomes.[385] Comparisons are made between those who are and are not exposed or different categories of exposure.[386] The main objective of a cohort study is to determine the prognosis and natural history of a disease or condition; there are two types of cohort studies open and closed.[387] Researchers use case-control

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[382] Röhrig, Baptist du Prel, Wachtlin and Blettner. "Types of Study in Medical Research" 265.

[383] Secondary data analysis is when a researcher utilizes data collected for another reason, a common secondary data analysis is Medicare and Medicaid information and laboratory results from a clinical trial. Cases reports are write-ups of a patients course of treatment.

[384] Röhrig, Baptist du Prel, Wachtlin and Blettner. "Types of Study in Medical Research" 265.

[385] Jan P. Vandenbroucke, et al. "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration." *Epidemiology* (Cambridge, Mass.) 18, no. 6 (November 2007): 805–35, 807. doi:10.1097/EDE.0b013e3181577511.

[386] Ibid.

[387] Laurie K. Twells. "Evidence-Based Decision-Making 1: Critical Appraisal." *Methods in Molecular Biology* 1281 (2015): 385–96, 393. doi:10.1007/978-1-4939-2428-8_23.

studies to compare exposures between people with and without a particular outcome.[388] The main objective of case-control studies is to identify causal factors and adverse effects of treatment and disease.[389] An example of a case-control study would be the number of influenza infections in patients with asthma who had (case) and had not (control) received the seasonal influenza vaccine.

Researchers assess the prevalence of exposures and other risk factors for disease in cross-sectional studies.[390] All individuals in the sample are evaluated at the same time points.[391] Ecological studies compare clusters of people usually grouped based on their geographical location or temporal associations assign one exposure level for each distinct group and can provide a rough estimation of prevalence of disease within a population.[392]

Table 2: Summary of Research Types, Objectives, and Influenza Examples

Type of Research	**Main Objective**	**Influenza Example**
Randomized Controlled Trial	Evaluate impact of intervention in the study population	Single dose influenza vaccination vs. two dose regime in vaccine naïve children.
Observational Therapy	Evaluate impact of intervention in the study population	Rates of influenza infection in children whose parents chose not to vaccinate.
Observational Prognosis	Impact other health factors on disease progression	Rates of patients with COPD being hospitalization with influenza infections.
Observational Diagnosis	Evaluate factors impacting diagnosis of the condition	Number of specimens collected from patients with

[388] Vandenbroucke, et al. "Strengthening the Reporting of Observational Studies in Epidemiology" 807.

[389] Twells "Evidence-Based Decision-Making 1: Critical Appraisal" 292.

[390] Vandenbroucke, et al. "Strengthening the Reporting of Observational Studies in Epidemiology" 807.

[391] Vandenbroucke, et al. "Strengthening the Reporting of Observational Studies in Epidemiology" 807.

[392] Matthew S. Thiese. "Observational and Interventional Study Design Types; an Overview." Biochemia Medica 24, no. 2 (January 2014): 199–210. doi:10.11613/BM.2014.022.

		Influenza Like Illness when the doctor did not request vaccination information.
Secondary Data Analysis	Re-use of existing data set	Number of deaths in Medicare patients hospitalization with pneumonia who received the influenza vaccine.
Case Report	Describes the problem and course of treatment of a patient or series of patients	The course of treatment for pregnant women hospitalized with influenza.
Interventional Epidemiological	Impact of a change in a disease over time	Rates of school absenteeism after in-school vaccination program.
Cohort	Study the natural progression of the condition	The incidence of influenza cases in a daycare facility.
Case-Control	Identify potential casual factors or study adverse effects	The incidence of influenza infection in asthma patients with and without influenza vaccination.
Cross-Sectional	Determine the prevalence of disease or other risk factors based on a sampling of the population.	Number of nurses who receive the influenza vaccination from work sponsored programs.
Ecological	Determine the prevalence and incidence of disease	Number of influenza infections over a period of time during work sponsored influenza vaccination programs.

Secondary research compiles results of primary research into a single data source. Policymakers often rely on secondary research due to its ability to combine multiple sources into a single document. Secondary research helps address the accessibility concerns highlighted in chapter two by collating data into one source. A meta-analysis uses statistical techniques to integrate and summarize the results of the included studies. The objective of a meta-analysis is to use a pre-defined protocol to complete a statistical

analysis of the quantitative data from the studies identified by a systematic review.[393] A systematic review collates all empirical evidence to answer a specific research question. Systematic reviews are characterized by clearly stated objectives, explicit, reproducible search methodology, an assessment of the validity of the findings, systematic presentation and synthesis of the characteristics and findings of the included studies.[394] Unfortunately, systematic reviews and meta-analysis are only as valuable as the studies included within them. Systematic reviews and meta-analysis which are based on poorly designed or executed research will have inaccurate results.

Research is integral to keeping pace with the ever-changing natural world. As the influenza virus evolves, research must continue to develop new vaccines and antivirals for epidemic and pandemic control. All types of research are valuable for providing a comprehensive evaluation of the epidemiology of the influenza virus and the efficacy of the influenza vaccine. Providing a comprehensive evaluation of both the virus and the vaccine is necessary for evidence-based policy. Research should undergo a systematic evaluation to ensure quality and applicability to the question at hand prior to being utilized in policymaking. The evaluation of research quality improves trust in the policymaking process and recommendation therapies and also improves the overall research enterprise.

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[393] Laurie K. Twells, "Evidence-Based Decision-Making 1: Critical Appraisal," *Methods in Molecular Biology* 1281 (2015): 385–96, 393. doi:10.1007/978-1-4939-2428-8_23.

[394] Alessandro Liberati, at el,. "The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Healthcare Interventions: Explanation and Elaboration." *BMJ* (Clinical Research Ed.) 339 (January 2009): b2700. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2714672&tool=pmcentrez&rendertype=abstract.

EVIDENCE BASE FOR RECOMMENDATIONS

The evidence base for target-population recommendations is important for three reasons. First, policymakers have a responsibility to ensure that their recommendations are appropriate and ethical. Second, a high-quality evidence base will help bolster public trust in the policy and the recommended intervention. Finally, analyzing the evidence base highlights knowledge gaps and encourages pertinent research. This section has three goals. First, is to establish that currently available randomized controlled trials are insufficient to provide the evidence for target-population recommendations. Second, to determine the types of evidence used by the CDC in making target-population recommendations. Finally, the presentation of evidence using the GRADE tables published with the 2012 WHO recommendations will be evaluated to determine if they are adequate to explain the rationale for the recommendations.

As introduced in chapter two, randomized controlled trials are the gold standard for clinical research; however, I assert they are insufficient for providing the complete evidence base for vaccine efficacy. This is because of the intrinsic difficulties in studying influenza due to timing, ethics, and small sample size. The cyclic activity of influenza combined with the changes in the circulating viruses from year-to-year creates a short window of time to recruit and complete studies often leading to small sample sizes. It is difficult to establish if a high efficacy rate is due to low circulation or a good virus-vaccine match. Placebo-controlled trials which withhold the standard of care (the influenza vaccine) are unethical, especially in high-risk populations.

Systematic Review of Influenza Vaccine Trials

A systematic review of randomized, controlled influenza efficacy studies was completed with the objective to identify the clinical endpoints of influenza vaccine efficacy studies. The goal of this review was to determine the number of meaningful public health outcomes used in influenza research and if those outcomes tracked with the target-population recommendations.[395] The electronic literature search was completed on July 6, 2015, applying the Patient, Population, Intervention, Comparator, Outcome, Timing and Settings (PICOTS) framework as outlined in the appendix. Inclusion criteria were: prospective, randomized-controlled trials, written in English, address vaccine efficacy via laboratory confirmed influenza infection and published 1980 and 2015. Electronic search strategies were developed and tested through an iterative process by an experienced medical information specialist in consultation with the review team. The databases searched were PubMed and the CENTRAL database of the Cochrane Library on Wiley. The full search criteria are listed in full in the appendix. This review is admitted limited by the use of only two reviewers.

RESULTS

Of 3,494 articles identified with the search criteria, 59 articles were identified as eligible for inclusion in the review. The majority (43) of the trials were conducted in high-income countries with the United States being the most common location. Of the 59 studies, only one included influenza-associated pneumonia, hospitalization, or death as a

[395] This systematic review was completed during my internship at the WHO during the summer of 2015. Special thanks and appreciation is due to Dr. Justin Ortiz, medical director in the Initiative for Vaccine Development, for his mentorship on this project. The analysis is my own and does not reflect the position or policy of the WHO IVR.

primary endpoint and four included these severe outcomes as a secondary endpoint. Laboratory-confirmed influenza was the primary endpoint in thirty-nine studies. Symptomatic laboratory-confirmed influenza was the required endpoint in eleven studies. The remaining nine studies had endpoints based upon serological responses (6) or other clinical outcomes (3). Note, the endpoints were what was defined in the article as the endpoint of the study; researchers may have also looked at other endpoints but chose not to publish them. The majority of studies were conducted using healthy adults (17) and healthy children (18). Only four studies enrolled adults with chronic diseases and two enrolled children with chronic diseases. Elderly patients were specified as the patient population in four studies and nursing home patients in two studies. Pregnant participants were included in only one study. Healthcare workers were presented in three studies.

DISCUSSION

Existing influenza vaccine RCTs do not evaluate the efficacy of the influenza vaccine in preventing severe outcomes. The implication of these findings is that few researchers are looking for serious illness in influenza trials; therefore, RCTs alone do not provide sufficient evidence to support the goal of the target-population recommendations, preventing severe illness and premature death. This is not to claim that other outcomes are not important; only to illustrate that the currently available randomized controlled trials do not support the claim that the influenza vaccine prevents serious illness and death in any population, let alone the target-populations.

Primary and secondary endpoints were analyzed to determine the severity of the illness being studied in randomized controlled influenza vaccine efficacy trials. Studies were categorized as follows:

Laboratory confirmed influenza: PCR-confirmed influenza or a combination of culture/PCR-confirmed influenza; and/or a four-fold increase in titer without mention of symptoms in the endpoint definition.

Symptomatic laboratory-confirmed influenza: Culture confirmation of influenza and clinical illness.

Serological Response: Increase in titer level without mention of culture or PCR confirmation.

Severe Outcomes Influenza-associated pneumonia, hospitalization, or death.

Other Clinical Outcome- Ear infections, other viral respiratory infections, etc.

Other Outcome: Safety and workplace absenteeism

Thirty-nine of the studies used laboratory-confirmed influenza as a primary endpoint. Symptomatic laboratory-confirmed influenza was reported as the primary endpoint in eleven studies. This is considered a more valuable endpoint from a public health standpoint because it evaluates not only when the presence of the influenza virus but also when people experience clinical symptoms bothersome enough to report. However, participants were likely experiencing symptoms in at least some of the studies using laboratory-confirmed influenza as an endpoint. This illustrated the need for standardized endpoint definitions, although this is beyond the scope of this project. Six studies reported serological response as the primary endpoint and seven as a secondary endpoint. Severe outcomes were reported as a primary endpoint in only one study and as a secondary endpoint in four other studies. Other endpoints included safety and work absenteeism. Other clinical outcomes were reported as an endpoint in ten studies, measured the incidents of non-influenza illnesses such as acute otitis media or upper respiratory infections. By not evaluating the prevention of severe outcomes in influenza vaccine use, RCTs do not adequately support the target-population recommendations on their own and may lend incidental support to the claims that the influenza vaccine is not effective, and the influenza virus does not cause severe illness.

Population	Number of Studies
Healthcare Workers	3
Families	4
Children with Chronic Disease	2
Adults with Chronic Disease	4
Elderly with Chronic Disease	1
Elderly	5
Pregnant Women	1
Healthy Adults	17
Healthy Children	18
Healthy Adults and Children	3
Not Reported	1

Table 3: RCTs Participant Populations

Participants in RCTs do not adequately reflect the target-populations. The majority of studies were conducted using healthy adults (17) and healthy children (18). Only four studies enrolled adults with chronic diseases and two enrolled children with chronic diseases. Elderly patients were specified as the patient population in four studies and nursing home patients in two studies. Pregnant participants were enrolled in only one study. Healthcare workers were enrolled in three studies. Families with children were evaluated in four studies. Comparing these available studies to the target-population recommendations is concerning because it highlights the lack of research being done in at-risk populations. While RCTs are challenging to complete for influenza vaccines, if RCTs are going to be the gold standard then they must be completed in all populations or other research must be fully accepted as a surrogate.

The results of this review support the claim that randomized clinical trials alone are not sufficient to support the current target-population recommendations. The stated purpose of the influenza vaccination is to prevent severe illness and death. However, very few randomized controlled trials are studying severe outcomes or the populations most at risk for those outcomes. The lack of severe outcomes being studied and studied in target-

populations makes it difficult for policymakers and the public to appreciate the value of the influenza vaccine based solely on RCTs, a more comprehensive research strategy is needed.

CDC Evidence

The CDC publishes a reference list with each yearly influenza vaccine recommendation. Their references support the target-populations themselves as well as the vaccine formulation and virus epidemiology. As the below table indicates, the number of references used by ACIP increased steadily until the 2010 when the ACIP issued the universal vaccination recommendation.

Table 4: Number of CDC References Used by Year

Year	Number of References
2002	287
2003	321
2004	336
2005	349
2006	376
2007	473
2008	502
2009	454
2010	552
2011	35
2012	26

Table Source: 2002-2012 CDC Influenza Recommendations

The 2005 references were analyzed to determine the types of studies upon which the ACIP based its' recommendations. The purpose of this analysis is two-fold, first to determine which types of research the ACIP considers valuable enough to consider in making recommendations. Second, is to provide the foundation for determining which

types of research the evaluation methodologies must be capable of fully and fairly evaluating. The year 2005 was chosen because it is the midpoint between 2002 and when the universal recommendations were issued in 2010 and in recognition of the fact that many of the citations are repeated each year.

Citations were retrieved from PubMed or university library sources to analyze the reference utilitzed by the ACIP. The study type was identified based on a review of the title, abstract, and/or text of the article. Of the 349 references, nine were unavailable via the University of Texas Medical Branch online sources. The three most common sources were randomized controlled trials (51), basic science studies (31), government reports (28), observational therapy studies (22), and case reports (21). The randomized controlled trials included many of the same RCTs found in the systematic review discussed above; thus having the same concerns of being concentrated in high-income countries with healthy populations and not being representative of the target-populations. Government reports included not only prior years but also commissioned reports regarding immunization of healthcare workers, national health promotion, and cost-effectiveness of influenza vaccination among others.[396] Review and inclusion of this type of evidence show the commitment of the ACIP to ensure that their recommendations have a robust evidence base. The inclusion of these research types in consideration of target-population recommendations is important because they appear to provide a complete consideration

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[396] National Foundation for Infectious Diseases. Call to action: influenza immunization among health-care personnel, 2003. Bethesda, MD: National Foundation for Infectious Diseases; 2003. Available at http://www.nfid.org.; US Department of Health and Human Services. Healthy People 2000: national health promotion and disease prevention objectives---full report, with commentary. Washington, DC: US Department of Health and Human Services, Public Health Service; 1991.; Office of Technology Assessment. Cost effectiveness of influenza vaccination. In: U.S. Congress. Washington, DC: Office of Technology Assessment; 1981.

of the influenza vaccine research. Observational studies provide insight that RCTs do not; how the influenza vaccine is used in the clinical setting outside of trial settings. Neither observational nor RCTs can provide the required evidence for target-population recommendations in isolation; all research must be considered and evaluated in a comprehensive manner.

WHO GRADE Tables

The GRADE methodology, discussed in greater detail in the next section, includes the use of Summary of Findings (SoF) tables to consolidate and communicate evaluation of the evidence. While SoF tables are not an absolute requirement of GRADE, they are considered an "invaluable tool for providing a succinct, accessible, transparent evidence summary for patients, health care providers, and policy makers."[397] The communication of the evidence evaluation is important for two reasons; first, it provides a more accessible route to the information upon which the recommendations are based. The WHO began using the GRADE methodology in all official position statements in 2007. As discussed in chapter two, a challenge to the creation of evidence-based policy is the inaccessible of research to policymakers due to both language (overuse of jargon) and limited resources for research. The Summary of Findings table is meant to allow the evidence to be presented in a manner that, ideally, makes the rationale for the recommendation clear. Second, the Summary of Findings table allows a more transparent decision-making process by outlining what outcomes were being evaluated, how the evidence was rated, and how that evidence impacted the final recommendations. This

[397] Guyatt, et al. "GRADE Guidelines: 12" 171.

transparency helps hold researchers and policymakers more accountable to each other and the public for the creation of sound, ethical policy based on science instead of politics. The 2012 influenza position paper includes citations, and the GRADE tables are available via the SAGE website.

The SAGE WG evaluated outcomes in seven different populations: pregnant women, infants, children (6 months to 2 years and 2 to 6 years), individuals over 65, individuals with asthma, HIV positive individuals, healthcare workers, and the impact of healthcare worker vaccination on the elderly. These evaluations provide valuable insight as to the rationale behind the target-population recommendations but are not readily accessible to the lay public.

The SoF Tables assume that the reader has a deep familiarity with the GRADE process and criteria; without this knowledge, the tables are ineffective at best and misleading at worst. Each outcome is separated into its own table and uploaded to the website separately, making consideration of the tables in conjunction with each other difficult. When reviewing the SoF Tables, the rationale for including pregnant women, the elderly, and patients with chronic conditions in the target-population recommendation appears to be questionable based on the evidence rating and statements on the quality of evidence.[398] While the SoF Tables provide an adequate summary for those familiar with the GRADE process, they should not be used to communicate the rationale for recommendations to the public or summary research for policymakers.

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[398] Maternal influenza evidence as rated as 2, with a limited confidence in estimated effect. Elderly evidence is rated as 1 (because if cannot be rated as a 0), with a low confidence in estimated effect. Evidence for effectiveness in HIV-infected adults is rated as 1 (again because it cannot be rated as a 0) with low confidence in estimated effect.

Maternal influenza immunization shows how SoF tables do not paint the full picture of the evidence evaluation in comparison to the recommendations. The recommendation to include pregnant women was made despite limited confidence in the estimate of effect and no information on vaccine efficacy or impact of laboratory-confirmed influenza infections in pregnant women.[399] However, the recommendation that pregnant women be vaccinated was based on the high quality of evidence of favorable newborn outcomes. This is difficult to piece together as the maternal and infant outcomes are presented in separate tables. The evidence evaluated to support the maternal indication included one randomized controlled study, one immunogenicity/safety RCT, and several observational studies with varying methodological limitations.[400] The evidence to support the safety of the influenza vaccine during pregnancy is considered low.[401] The evidence to support maternal immunization for the protection of infants under the age of six months was

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[399] SAGE Working Group. "SAGE GRADE Table 1a: Pregnant Women, Maternal Outcomes." *Immunization, Vaccines and Biologicals Influenza Position Paper*, 2012. http://www.who.int/immunization/position_papers/influenza_grad_maternal_outcomes.pdf?ua=1.

[400] Ibid.; Steven B, Black, et al. "Effectiveness of Influenza Vaccine during Pregnancy in Preventing Hospitalizations and Outpatient Visits for Respiratory Illness in Pregnant Women and Their Infants." *American Journal of Perinatology* 21, no. 6 (August 2004): 333–39. doi:10.1055/s-2004-831888.; A.S. Deinard, and P Ogburn. "A/NJ/8/76 Influenza Vaccination Program: Effects on Maternal Health and Pregnancy Outcome." *American Journal of Obstetrics and Gynecology* 140, no. 3 (June 1, 1981): 240–45. http://www.ncbi.nlm.nih.gov/pubmed/7246624.; J.A. Englund, et al. "Maternal Immunization with Influenza or Tetanus Toxoid Vaccine for Passive Antibody Protection in Young Infants." *The Journal of Infectious Diseases* 168, no. 3 (September 1993): 647–56. http://www.ncbi.nlm.nih.gov/pubmed/8354906.; Madoka Horiya, et al. "Efficacy of Double Vaccination with the 2009 Pandemic Influenza A (H1N1) Vaccine during Pregnancy." *Obstetrics and Gynecology* 118, no. 4 (October 2011): 887–94. doi:10.1097/AOG.0b013e31822e5c02. J. F.Hulka, "Effectiveness of Polyvalent Influenza Vaccine in Pregnancy. Report of a Controlled Study during an Outbreak of Asian Influenza*." Obstetrics and Gynecology*, 23 (1964): 830-7.

[401] SAGE Working Group. "SAGE GRADE Table 6: Safety of Inactivated Influenza Vaccine in Pregnant Women." *Immunization, Vaccines and Biologicals Influenza Position Paper*, 2012. http://www.who.int/immunization/position_papers/influenza_grad_safety_pregnancy.pdf?ua=1.

stronger than that to support immunization in pregnant women.[402] Five observational studies that showed vaccination of mothers during pregnancy reduced lab-confirmed influenza rate in infants under 6 months of age compared to non-vaccinated mothers.[403] Therefore, the confidence in the effect of maternal influenza vaccine on infants was high. While influenza vaccination may not have a confirmed effected on pregnant women the positive impact on newborns, especially infants who cannot receive the influenza vaccine until they are six months old, warrants the recommendation that pregnant women be vaccinated.

The WHO has been criticized for using low-quality evidence for recommendations as this is inconsistent with GRADE guidance.[404] This criticism indicates a lack of understanding in the GRADE research standard for recommendations and a lack of communication in the rationale. Per the GRADE guidelines on recommendations, the research is just one of five elements that determinants of the strength of the recommendations.[405] Panels also look at the balance between desirable and undesirable effect, values, and preferences surrounding the intervention and the costs of the intervention. Evidence must be looked at in the context of its application in order to be appropriately evaluated.

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[402] SAGE Working Group. "SAGE GRADE Table 1b: TIV in Pregnant Women: Infant Outcomes." *Immunization, Vaccines and Biologicals Influenza Position Paper*, 2012. http://www.who.int/immunization/position_papers/influenza_grad_infant_outcomes.pdf?ua=1.

[403] SAGE Working Group. "SAGE GRADE Table 1b: TIV in Pregnant Women: Infant Outcomes." *Immunization, Vaccines and Biologicals Influenza Position Paper*, 2012. http://www.who.int/immunization/position_papers/influenza_grad_infant_outcomes.pdf?ua=1.

[404] Paul E. Alexander, et al. "World Health Organization Strong Recommendations Based on Low-Quality Evidence (Study Quality) Are Frequent and Often Inconsistent with GRADE Guidance." *Journal of Clinical Epidemiology*, December 19, 2014. doi:10.1016/j.jclinepi.2014.10.011.

[405] Gordon H. Guyatt., etl al.. "Going from Evidence to Recommendations." *BMJ (Clinical Research Ed.)* 336, no. 7652 (May 10, 2008): 1049–51. doi:10.1136/bmj.39493.646875.AE.

Target-population recommendations for the influenza vaccines have evolved with changes in the available research. However, the evidence and recommendation are still poorly communicated. As will be discussed in the following section, research evaluation methodologies favor RCTs leading to bias against observational studies.

EVALUATING RESEARCH QUALITY

Research can, and should, be used to shape policy because policy impacts the lives of citizens. Therefore, it is imperative that the highest quality research is used to shape policy. Evaluating research may seem paradoxical. If we, as a society, trust researchers to experiment on humans do we not trust them to do so in a manner that creates high-quality results? If we must evaluate the result, should we be trusting the researchers to complete the studies at all? While the ethical issues of research will be discussed in a later chapter, the short answer is yes- we, as a society, trust researchers but also have a responsibility to ensure that the research is free of bias and reaches certain standards. Researchers rarely intentionally produce misleading or inaccurate results.[406] However, mistakes do happen, and biases can go undetected. Evaluating research prior to relying on its results in the policymaking process provides an additional level of protection for the public and encourages trust not only in the policy itself but also in the

[406] Institute of Medicine. *Conflict of Interest in Medical Research, Education, and Practice.* Edited by Bernard Lo and Marilyn Fields. Conflict of Interest in Medical Research, Education, and Practice. Washington, DC: National Academies Press, 2009. http://www.ncbi.nlm.nih.gov/pubmed/20662118.

intervention. Evaluating research requires a transparent, and systematic approach. GRADE has become the standard research evaluation methodology in recent years, although it still suffers inadequacies. This section will discuss the available research evaluation methodologies and their application to the evidence base for target-population recommendations.

Research evaluation methodologies have a clear preference for RCTs. I argue that this preference is problematic in evaluating influenza vaccine research for three reasons. First, this preference undervalues research giving critical information simply because it is using an alternative study methodology. A well-designed and executed observation trial is more valuable in determining efficacy than a poorly designed RCT. Second, the preference can be potential misleading on the strength of research supporting a recommendation. As discussed in the previous section, the ratings of the maternal influenza vaccine studies were low; leading to the potential conclusion pregnant women should not be included in the target-populations. Finally, because the ACIP uses such a wide breadth of research types, evaluation methodologies that have such a clear preference for RCTs are unable to evaluate the evidence base for target-population recommendations accurately.

The United States Preventative Service Task Force (USPSTF) was created in 1984 as an independent, volunteer panel with the mission to "improve the health of all Americans by making evidence-based recommendations on clinical preventive services and health promotion in primary care settings."[407] USPSTF provides a thorough

[407] Albert Siu, and Michael LeFevre. "U.S. Preventative Services Task Force Procedure Manual," (December 2015) i.

evaluation methodology that could be adopted for evaluating influenza vaccine studies. Where the USPSTF methodology excels is providing specific study criteria and applicability assessments. I argue that the methodology is limited by a lack of flexibility for considering well-designed observational studies as higher levels of evidence.

Research Evaluation Methodologies

USPSTF, like most other research evaluation methodologies, considers RCTs "the ideal for questions regarding benefits or harms of various intervention."[408] USPSTF uses both a general hierarchy of research design and specific criteria to evaluate research. Properly powered and conducted RCTs, well-conducted systematic reviews and meta-analysis of homogenous RCTs reside at the top of the hierarchy of research design.[409] Well-designed controlled trials without randomization and well-designed cohort or case-controlled analysis studies follow as second and third tiers in the hierarchy.[410] The fourth tier of evidence consists of observational studies that yield results of large magnitude.[411] Opinions of respected researchers and clinicians, often based on clinical experience, descriptive studies or case reports, and reports of expert committees make up the bottom tier of the hierarchy of research evidence.[412] This hierarchy is similar throughout all research evaluation methodologies and reflecting RCTs as the standard of evidence.

Specific criteria for each type of study guide the evaluation. Studies are rated as good, fair, and poor. Studies that are rated 'good' provide evidence that consistently

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[408] Ibid., 27.
[409] Ibid.
[410] Ibid.
[411] Ibid.
[412] Ibid.

results from "well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes."[413] 'Fair' studies provide evidence that is sufficient to determine effects on health outcomes, but the strength of the evidence is limited, either in quality or consistency.[414] When the evidence is insufficient to assess the effects on health outcomes, due to the power of studies, flaws in the design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes then the study is rated as 'poor.'[415] Study specific criteria are available in the appendix of this chapter.

Once the assessment of the studies is complete the USPSTF abstracts and synthesize the data from the studies, then drafts a final evidence report. The evidence report summarizes the findings and describes the evidence for the key questions of the recommendations. Evidence for key questions is rated as either convincing, adequate or inadequate based upon the quality of the studies found in the review.[416] Convincing evidence comes from "well-conducted studies of appropriate design that demonstrate consistent and precise results focused on outcomes and generalizable to the intended US primary care population and setting."[417] When significant limitations in study design, quality, overall applicability, and heterogeneity are present, evidence for the key

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[413] U.S. Preventive Services Task Force. "Grade Definitions." Accessed April 4, 2016. http://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions#grade-definitions-after-july-2012.

[414] Ibid.

[415] Ibid.

[416] Ibid., 38. Assessment of the studies also includes the applicability assessment to the primary care setting in the United States, meaning if the intervention could be successfully completed by primary care physicians within the office setting.

[417] Ibid.

question is considered adequate.[418] The evidence is considered inadequate when there is a complete lack of evidence, or the evidence contains a fatal flaw.[419] The USPSTF uses the final evidence report to draft its recommendations on preventative services. While the USPSTF could make recommendations on influenza vaccinations; it defers vaccination recommendations to the ACIP. This referral is made due to the ACIP's resources for timely updates of the evidence and a scientifically acceptable methodology for review that includes assessment of benefits and harms that the Taskforce judges to be adequate for the topic.[420]

The "Rules of Evidence and Clinical Recommendations on the Use of Antithrombotic Agents" was published in *Chest* in October 1992 to provide evidence-based guidance for clinicians on the treatment and prevention of blood clots and stroke.[421] The authors determined a consensus approach was needed due to the range of treatment decisions and the placebo effect on both the patient and the clinician.[422] Basing recommendations on the results of "rigorously controlled investigations" was thought to lead to better clinical outcomes for patients. While the rules of evidence were not intended for vaccine use, the spirit behind them, to base a clinical decision on high-quality evidence, are in line with the target-population recommendation. However, the rules themselves would not result in a balanced or accurate evaluation of the target-population recommendation evidence base due to the preference for RCTs. Under these

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[418] Ibid.

[419] Ibid. A fatal flaw occurs when there is evidence of severe bias i.e. not reporting randomization or large differences in baselines.

[420] Ibid., 17.

[421] Debroah J. Cook, Gordon H. Guyatt, Andreas Laupacis, and David L. Sackett. "Rules of Evidence and Clinical Recommendations on the Use of Antithrombotic Agents." *Chest* 102, no. 4 Suppl (October 1992): 305S – 311S. http://www.ncbi.nlm.nih.gov/pubmed/1395818.

[422] Ibid.

rules of evidence, studies are evaluated in three categories: validity, importance, and relevance.[423] Valid studies are randomized, blinded and have all patients accounted for throughout the study.[424] Importance is determined based upon the statistical and clinical significance of the results.[425] Studies are relevant if clinically important outcomes are reported, the study patients are similar, and the therapeutic intervention is feasible.[426] The authors developed five levels of evidence:

> Level 1: Randomized trials with low false-positive and low false-negative errors (high power) [trial demonstrated a statistically significant benefit]
> Level II: Randomized trials with high false-positive and/or high false-negative errors (low power) [trial demonstrated no effect of therapy but was large enough to exclude possibility of clinically important benefit]
> Level III: Nonrandomized concurrent cohort comparisons between contemporaneous patients who did and did not receive antithrombotic agents
> Level IV: Nonrandomized historical cohort comparisons between current patients who did receive antithrombotic agents and former patients who did not
> Level V: Case series without control subjects.[427]

RCTs are the preferred methods of evaluation, leading to Level 1 and 2 evidence. The authors support the use of reviews and meta-analysis because primary studies are limited by inadequate sample size, pooling data from multiple sources allows for conclusions to be drawn in higher confidence if those conclusions are drawn from studies using level 1 or 2 evidence. A limitation of this methods is that does not take into consideration the fact that epidemiological or observational studies may be the best, or only, way to evaluate an intervention in a given population.

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[423] Ibid., 306S.
[424] Ibid.
[425] Ibid.
[426] Ibid.
[427] Ibid.

These evidence levels were not designed with vaccine use in mind. Therefore, it is not surprising that adjustments to the methodology would be needed in order to utilize this method for vaccines. Validity, importance, and relevance are three important criteria for evaluating the use of a study both generally and in the context of policymaking. Although the authors give validity criteria specifically for RCTs, other research types have validity requirements as well. Using these criteria without the preference toward RCTs would vastly improve the methodology.

The Oxford Centre for Evidence-Based Medicine released its methodology in 2000 and updated it in 2011. This is a tool designed for use in conjunction with traditional critical appraisal in busy environments where highly technical; resource-intensive tools may not be practical.[428] It is meant to be a hierarchy of what the best evidence for a particular issue is and does not provide a full evaluation scheme.[429] The Oxford Centre's tool for clinicians and policymakers to help identify sources of information but because it does not provide a true methodology its value is limited. Level 1 evidence is systematic reviews for all questions on diagnosis, prognosis, and treatment.[430] Individual randomized trials or well- designed observational studies are Level 2 evidence for questions concerning prognosis and treatments. This is the only methodology that places RCTs and well-designed observational studies at the same level of evidence. Cross-sectional studies with consistent reference standards and blinding are

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[428] Jeremy Howick, et al. "Background Document: Explanation of the 2011 Oxford Centre for Evidence-Based Medicine Levels of Evidence." Center for Evidence Based Medicine, 2011. http://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-Background-Document-2.1.pdf.

[429] Ibid.

[430] Jeremy Howick, et al. "The 2011 Oxford CEMB Evidence Level of Evidence (Introductory Document)." Oxford Center for Evidence-Based Medicine, 2011. http://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-Introduction-2.1.pdf.

used as Level 2 evidence in issues concerning diagnosis.[431] Non-randomized trials, case-control studies, and mechanism-based reasoning make up Levels 3, 4, and 5.[432] The Oxford Centre relies on well-designed systematic reviews as the highest evidence level for most questions under the presumption that these reviews will collate the best information available.

The major limitation of evidence evaluation methodologies is their preference for RCTs to the disadvantage of other research methods. While RCTs are the gold standard in clinical research, they are not the only type of research being done and are not necessarily the best type of study for vaccine research, as discussed earlier in this chapter. Research that provides a comprehensive evaluation of the disease and the intervention being considered is needed by both policymakers and the public; the evidence evaluation methodology needs to be able adequately to consider all types of research.

Checklists

Checklists are another tool for assessing research. Checklists are not designed with the express purpose of evaluating research; instead, are used to assist researchers in drafting protocols and communicating findings via articles. However, checklists do assist in evaluating research by ensuring that basic guidelines are met. While multiple checklists for every type of research are available, I have chosen the to focus on checklists endorsed by the Patient-Center Outcomes Research Institute (PCORI). PCORI is an independent, nonprofit organization with the Congressionally authorized mandate to

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[431] Ibid.

[432] Ibid. Mechanism-based reasoning is defined by the Oxford CEMB as a claim that an intervention produces a patient relevant outcome.

"improve the quality and relevance of evidence available to help patients, caregivers, clinicians, employers, insurers, and policymakers make informed health decisions."[433] In 2014, PCORI issued a methodology report outlining forty-seven methodology standards and their justifications for use; the checklists discussed here are included in these standards.[434]

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) initiative was launched in 2007.The aim was to improve the completeness of trial protocols by producing evidence-based recommendations on a minimum set of items to be addressed in protocols.[435] The guidelines for protocol content that existed at the time varied in scope and seldom involved empiric evidence or stakeholder consultation.[436] The SPIRIT checklist is meant to promote transparency and lead to a more robust description of the research planned. Although it is not meant to judge trial quality, "A well-written protocol facilitates an appropriate assessment of scientific, ethical, and safety issues before a trial begins; consistency and rigor of trial conduct; and full appraisal of the conduct and results after trial completion."[437] Improving protocol quality and completeness has the added benefit of increasing increase efficiency of protocol review by IRBs and thus the efficiency of research generally.[438]

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[433] Patient Centered Outcomes Research Institute. "About Us | PCORI." Updated October 6, 2014. Accessed April 8, 2016. http://www.pcori.org/about-us.

[434] PCORI Methodology Committee. "The PCORI Methodology Report." (November 2013) Accessed April 8, 2016. http://www.pcori.org/assets/2013/11/PCORI-Methodology-Report.pdf.

[435] An-Wen Chan, et al. "SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials." *Annals of Internal Medicine* 158, no. 3 (February 5, 2013): 200–207, 200. doi:10.7326/0003-4819-158-3-201302050-00583.

[436] Ibid., 200.

[437] Ibid., 200, 204.

[438] Ibid., 204.

Strengthening the Reporting of Observation Studies in Epidemiology (STROBE) was the result of an international, collaborative initiative of epidemiologists, methodologists, statisticians, researchers and journal editors involved in the conduct and dissemination of observational studies.[439] The STROBE checklist covers the three main types of observational studies: cohort, case-control, and cross-sectional.[440] STROBE was developed to assist researchers in providing more detailed reports of epidemiology studies. The aim was to "ensure a clear presentation of what was planned, done, and found in an observational study."[441]

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was published in 2009.[442] PRISMA, like most other checklists, was developed by a group of review authors, methodologists, clinicians, medical editors, and consumers. PRISMA focuses on assisting authors in reporting the results of a systematic review to assess the benefits and harms of a heath care intervention in a transparent and complete manner.[443]

Checklists are a valuable tool in research evaluation but cannot be used in isolation. Checklists are meant to assist researchers in crafting more transparent and robust protocols and reports. The benefit of assisting in the evaluation of research quality is secondary. Incorporating checklists into a comprehensive evidence evaluation

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[439] STROBE Group. "STROBE Statement: Home." Accessed April 4, 2016. http://www.strobe-statement.org/index.php?id=strobe-home.

[440] Jan P. Vandenbroucke, et al. "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration." *Epidemiology* (Cambridge, Mass.) 18, no. 6 (November 2007): 805–35, 806. doi:10.1097/EDE.0b013e3181577511

[441] Vandenbrouchke, et al., Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration." 805

[442] Alessandro Liberati, et al.. "The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions." *Annals of Internal Medicine* 151, no. 4 (2009): W65–94. doi:10.1371/journal.pmed.1000100.

[443] Ibid.

methodology would improve research evaluation by providing a framework for study specific criteria.

Evidence evaluation methodologies have two main weaknesses, the lack of flexibility and the over-reliance on RCTs. Methodologies tend to be based upon a standard hierarchy which places RCTs ahead of other research types.

Table 5: Summary of Evaluation Methodologies

USPSTF	**Rules of Evidence**	**Oxford**
Tier 1- RCTs, Systematic Reviews, Meta-analysis of homogeneous RCTs	Level 1- High powered RCTs	Level 1- Systematic Reviews
Tier 2- Well-designed controlled trials without randomization	Level 2- Low powered RCTs	Level 2- RCTs or well-designed observational studies
Tier 3- Well-designed cohort or case-controlled	Level 3- Nonrandomized concurrent cohort	Level 3- Non-randomized trials
Tier 4- Observational studies with large effects of magnitude	Level 4- Case Series	Level 4- Case-Control studies

Although the USPSTF is the most robust of the evaluation methodologies discussed here, it still suffers from inflexibility and lack of complete consideration of observational studies. While an observational study can be a good observational study, it cannot be rated as highly as an RCT, even if that RCT is poorly planned and executed. A comprehensive evidence evaluation needs to consider all types of research and provide a fair rating without a preference for RCTs. The ACIP used 349 sources for the 2005 influenza vaccine recommendations, only 51 of those were RCTs. Based on these evaluation methodologies, only 51 of the sources used by the ACIP have the possibility of being rated as high-quality evidence. This puts the recommendations at risk of being

viewed as supported by poor quality evidence or disregarded altogether. An evaluation methodology that does not have a de facto preference for RCTs would allow for a more accurate, comprehensive evaluation that better communicates the evidence available.

GRADE Methodology

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group began in 2000 to address the shortcomings of the grading systems and develop a single, "common sensible approach to evaluating the quality of evidence and strength of recommendations."[444] GRADE provides a more comprehensive evaluation of research than other methodologies by being more flexible in evaluating all research types. However, further adaptations of the methodology would be required to provide the ideal evaluation of influenza vaccine research. The purpose of the GRADE process is to provide a summary of the research and a quality rating for each outcome.[445] The evaluation and summary are conducted and communicated through the evidence profile and summary of findings table. The evidence profile is a detailed document that provides records of the judgments of each review regarding the quality of the studies. The summary of findings table is a meant for a wider audience and is often included as an appendix in the review or guideline. The table below lays out the evidence rating system used by GRADE:

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[444] GRADE Working Group. "GRADE Working Group: Frequently Asked Questions." Accessed April 11, 2016. http://www.gradeworkinggroup.org/FAQ/index.htm.

[445] Gordon H. Guyatt, et al. "GRADE Guidelines: 1. Introduction; GRADE Evidence Profiles and Summary of Findings Tables." *Journal of Clinical Epidemiology* 64, no. 4 (April 2011): 383–94, 386. doi:10.1016/j.jclinepi.2010.04.026.

Study Design	Quality of Evidence	Lower if	Higher if
Randomized	High	Risk of bias -1 Serious -2 Very Serious	Large Effect +1 Large +2 Very Large
	Moderate	Inconsistency -1 Serious -2 Very Serious	Dose Response +1 Evidence of a gradient
Observational	Low	Indirectness -1 Serious -2 Very Serious	All plausible confounding +1 would reduce a demonstrated effect or +1 would suggest a spurious effect when results so no effect
	Very Low	Imprecision -1 Serious -2 Very Serious Publication bias -1 Likely -2 Very Likely	

Table 6: GRADE Evidence Rating Source: Gordon H. Guyatt, et al. "GRADE Guidelines: 1. Introduction; GRADE Evidence Profiles and Summary of Findings Tables." *Journal of Clinical Epidemiology* 64, no. 4 (April 2011): 383–94, 386. doi:10.1016/j.jclinepi.2010.04.026.

GRADE automatically classifies randomized controlled trials higher than observational studies, although evidence quality can be up or downgraded during the evaluation process. The GRADE process calls for evidence to be evaluated on the bias, imprecision, inconsistency, and indirectness.

Bias can occur from due to in study design and conduct and publication. Flaws in study design or conduct can lead to misleading results; therefore, when the risk of bias is high the study should be viewed with caution. Bias includes lack of allocation or concealment, as well as the "lack of blinding, incomplete accounting of patients and

outcome events, selective outcome reporting, stopping early for benefit, use of unvalidated outcome measures, carryover effects," and recruitment bias in cluster-randomized trials.[446] The GRADE process uses four principles in determining the overall risk of bias. First, the quality of evidence is not averaged across studies, the contribution of each study must be considered.[447] Second, each study must be evaluated for the extent to which the trial contributes to the estimate of the magnitude of the effect.[448] Third, reviewers should be conservative in the judgment of rating down.[449] Finally, the risk of bias should be considered in the context of other limitations.[450]

Imprecision is measured by the confidence interval of the study.[451] Confidence intervals show the impact of random error on evidence quality. Confidence intervals represent the range of results if the experiment were repeated multiple times; the goal is a 95 percent confidence interval.[452] GRADE recommends that if the number of patients included in a review is less than a conventional well-powered trial that the review panel considers rating the study down a level for imprecision.[453] Influenza vaccine trials have a higher risk of downrating for imprecision because they tend to have a small sample size even when results are pooled in a review there may be fewer participants than in a conventional trial.

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[446] Gordon H Guyatt, et al. "GRADE Guidelines: 4. Rating the Quality of Evidence; study Limitations (Risk of Bias)." *Journal of Clinical Epidemiology* 64, no. 4 (April 2011): 407–15, 408. doi:10.1016/j.jclinepi.2010.07.017

[447] Ibid., 412.

[448] Ibid., 412.

[449] Ibid., 412.

[450] Ibid., 412.

[451] Gordon H. Guyatt, et al. "GRADE Guidelines 6. Rating the Quality of Evidence; imprecision." *Journal of Clinical Epidemiology* 64, no. 12 (December 2011): 1283–93. doi:10.1016/j.jclinepi.2011.01.012.

[452] Ibid., 1284.

[453] Ibid., 1287.

Evidence should apply directly to the outcomes being measured; indirect evidence is less valuable. Direct evidence is research that compares the intervention in the intended population and measures outcomes important to patients.[454] Indirectness is measured in applicability in the population, differences in interventions, surrogate outcomes, and indirect comparisons.[455] Differences in the population should not be rated down unless there is the reason that the biological differences in the populations would substantially impact the magnitude of the effect.[456] Differences in interventions must be considered including the resources of the setting.[457] For example, studies in high-income countries often do not reflect the resources available in lower or middle-income countries, and thus the results may not apply because the intervention may not be feasible. While GRADE does not specifically address health economic evaluations, the socioeconomic status of the area that the intervention will be used be considered. This is one of the reasons that the target-population recommendations differ between the WHO and CDC; the WHO must make recommendations that are flexible to the economic conditions of all member countries while the CDC makes recommendations for a resource-rich nation.

Evidence should apply to the outcomes as closely as possible. Outcomes are not uniform, and not all studies of a particular disease or intervention will study all outcomes. Some outcomes have acceptable surrogate measures, such as fractures for bone density, others do not; influenza-like-illness is not an acceptable surrogate for laboratory-

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[454] Gordon H. Guyatt, et al. "GRADE Guidelines: 8. Rating the Quality of Evidence; Indirectness." *Journal of Clinical Epidemiology* 64, no. 12 (April 11, 2011): 1303–10, 1304. doi:10.1016/j.jclinepi.2011.04.014.

[455] Ibid., 1304.

[456] Ibid., 1304-5.

[457] Ibid., 1305.

confirmed influenza infection. As mentioned earlier in this chapter, there is a need for standardized case definition in influenza research. Standardized case definition and outcomes would allow for more straightforward evaluation of the evidence. The magnitude of the difference between the surrogate and the desired outcome should determine the decision to rate down.[458] Indirect comparisons must be used when head-to-head comparisons are not simply not available.[459]

UP-RATING THE EVIDENCE

GRADE allows for exceptional evidence to be up-rated. This is the main difference between GRADE and its predecessors. The ability to increase the rating of exceptional research allows for a more balanced presentation of RCTS and observational studies. The increased rating of observational studies on the impact of maternal vaccination on infant outcomes provided the justification for the recommendation that pregnant women be included in the target-population recommendations. Up-rating should only be considered when all potentially limiting factors have been addressed.[460] There are three instances in which evidence should be considered for up-rating. First, when there is a large magnitude of effect.[461] A positive dose-response gradient is the second reason.[462] A positive dose-response gradient is the relationship between the intervention and the response; in influenza vaccines, this would be the relationship between the vaccine and

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[458] Ibid., 1306.
[459] Ibid., 1307.
[460] Gordon H. Guyatt, et al. "GRADE Guidelines: 9. Rating up the Quality of Evidence." Journal of Clinical Epidemiology 64, no. 12 (December 2011): 1311–16, 1312.. doi:10.1016/j.jclinepi.2011.06.004.1315
[461] Ibid., 1312.
[462] Ibid., 1313-1314.

the number of infections prevented. The final reason is when all possible confounders or other biases have been controlled leading to increased confidence in estimated effect.[463] The ability to uprate evidence is a key strength of the GRADE methodology in terms of influenza vaccine research. While GRADE automatically rates RCTs as higher quality than observational studies, exceptional observational studies may still be upgraded to high rating.

Once the individual studies have been evaluated, the overall body of evidence is considered. The overall rate of the evidence is determined by the best evidence available from the individual studies; if the best individual studies are moderate quality, then the body of evidence as a whole is moderate.[464]

LIMITATIONS OF GRADE

The GRADE process combines the strengths of many prior research evaluation methods but is not without limitations. The GRADE process is greatly dependent upon the expert opinion of the members of the review panel. Despite the robust process used by GRADE, the quality of evidence rating may differ between panels. There are three main areas where evidence rating is subjective. First is the outcomes; desirable and undesirable outcomes vary between geographic areas and experts leading to different thresholds of acceptability. For example, a panel of urban community health professionals may find that the influenza vaccine having a 70 percent efficacy in pregnant women to be an acceptable outcome while a panel of rural midwives may not. Differences in values and preferences could lead to a difference in the overall balance of

[463] Ibid., 1314.
[464] Guyatt, et al. "GRADE Guidelines: 4," 411.

desirable and undesirable outcomes and rating of confidence in estimates. Ratings of confidence may differ as a result of uncertainties in the risk profile of untreated populations. Although the GRADE process is the most comprehensive, broad-based evaluation methods, it is still subject to human influence.

The GRADE methodology is the best available method for evaluating research. I advocate for the use of the GRADE methodology not only because it is considered acceptable by the WHO and more than sixty other organizations but because, in comparison with other available methodologies, GRADE provides the most transparent, robust evaluation methodology that also takes into account the required flexibility for different types of research.

EVIDENCE EVALUATION BY WHO AND CDC

The WHO and CDC both use adaptions of the GRADE methodology to evaluation research prior to making recommendations. WHO began accompanying vaccine position papers and SAGE reports with GRADE Summary of Findings tables in April 2007.[465] The full process for issuing recommendations was discussed in chapter three and will not be repeated here.

The ACIP voted unanimously to adopt a framework for evaluating research based on the GRADE methodology during the October 2010 meeting.[466] This vote was based on the Evidence-Based Recommendation Work Group (EBRWG) review and critique of

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[465] Ibid., 3-4.

[466] Ahmed Faruque, et. al. "Methods for Developing Evidence-Based Recommendations by the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC)." *Vaccine* 29, no. 49 (November 15, 2011): 9171–76, 9172. doi:10.1016/j.vaccine.2011.08.005.

available methodologies. The EBRWG was tasked with developing or endorsing a framework which focused on transparency, was capable of evaluating evidence of varying strengths, considered both individual and community health and could be continuously improved and adapted.[467] In addition to GRADE, EBRWG reviewed methodologies from the American Academy of Pediatrics, The U.S. Preventative Services Task Force, and the National Advisory Committee on Immunization (Canada).[468] The GRADE methodology was chosen as the foundation for the framework due to acceptance by a number of organization including the American Academy of Family Physicians, Infectious Disease Society of America, UpToDate, Agency for Healthcare Research and Quality, and the WHO, and its applicability to the needs of the working group.

The ACIP labels recommendations as Category A and B as opposed to strong and weak.[469] Category A recommendations apply to all persons in age or risk group; Category B recommendations require individual clinical decision making.[470] ACIP has a four-tier hierarchy of evidence that is more detailed than GRADE offers:[471]

> (1) Randomized controlled trials (RCTs), or overwhelming evidence from observational studies.
> (2) Randomized controlled trials with important limitations or exceptionally strong evidence from observational studies.
> (3) Observational studies, or randomized controlled trials with notable limitations.
> (4) Clinical experience and observations, observational studies with important limitations, or randomized controlled trials with several major limitations.

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[467] Ibid.
[468] Ibid.
[469] Ibid., 9173.
[470] Ibid.
[471] Ibid.

ACIP's evidence levels are superior to GRADE's in that they take into account the limitations of the RCT and benefit of using observational trials.

Adapting the Evidence Evaluation Methodology for Vaccine Research

Influenza vaccine research requires an evaluation methodology that is capable of rating all research types in a transparent manner with the results of the evaluation easily communicated to all communities. The GRADE methodology provides an excellent starting point for crafting the ideal vaccine research evaluation methodology. I recommend four main changes to GRADE. First, the use of appropriate PCORI-endorsed checklists. While checklists do not evaluate quality per se, they do help ensure that certain reporting and conduct criteria are met. Utilizing the checklists within the evidence evaluation methodology provides an initial review to ensure that basic accepted fundamentals have been met. The de facto hierarchy would be removed to allow for level evaluation of research from the onset. Research would be evaluated based upon its quality of conduct and reporting without preference towards particular study types. Third, clear expectations of study quality, similar to the USPSTF, would be provided for each type of study. These criteria would spell out what is required for a study to be considered high, acceptable, low, or unacceptable; allowing for transparent evaluation. Finally, more detailed criteria for up and downgrading would need to be provided. While the GRADE methodology is a good starting point, additional work is needed to adapt the methodology to vaccine research.

The presentation and communication of the research review and evidence grading must be improved. While Summary of Findings Tables are helpful for those who are

familiar with the GRADE methodology, those who are not familiar with the methodology can be accidently misleading on the value of the research being used. I recommend that the tables be revised to include not only the numeric value of the rating but also an explanation of the value. The design of the table should be as standardized as possible based on the accepted evaluation criteria.

CONCLUSION

This chapter reviewed research types and evaluation methodologies in order to assess the need for changes to provide a balanced evaluation of influenza research. The first part of the chapter focused on defining research types, the populations and outcomes studies in RCT and the types of research used by the CDC. RCTs are considered the gold standard in clinical research for good reason; they provide excellent information when designed and executed properly. However, RCTs cannot provide the breadth of research needed to substantiate the target-population recommendations due to the ethical and logistical challenges of influenza research. The breadth of research used by the ACIP to develop the target-population recommendations allows for a comprehensive evaluation of the epidemiology of the influenza virus and the efficacy of the vaccine. The inclusion of observation studies such as cohort and case studies allows for a real world appraisal of the use and efficacy of the influenza vaccine in addition to the controlled trial. This real world provides vital information for researchers and policymakers alike, as was seen during the expansion of the ACIP indication for children. Surveillance studies showed that physicians were missing influenza diagnoses in children; to combat this problem, the indication for children was increased. However, these studies would not be rated as high levels of evidence under the current evaluation methodologies. The presentation of the

evidence and recommendations are inadequate at communicating the actual evidence used and the rationale behind the recommendations. This inadequate communication is due to the deep familiarity with GRADE methodology required to utilize the Summary of Findings tables. The inadequate presentation can lend accidental support to the belief that the influenza vaccine is not effective, and the virus itself does not cause serious illness. The second half of the chapter focused on research evaluation methodologies. I reviewed four evaluation methodologies currently in use, the United States Preventative Service Task Force, The Rules of Evidence and Clinical Recommendation on the Use of Antithrombotic Agents, the Oxford Centre for Evidence-Based Medicine, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE). I found that all current methodologies place RCTs at the top of their quality hierarchy, while I am not arguing against RCTs, the inability to have a well-designed, well-executed observational trial be rated highly is problematic for vaccine research. Current research evaluation methodologies are not able to provide a balanced appraisal of the evidence base for target-population recommendations without adaptations. Although not designed to evaluate the quality of research I also reviewed checklists supported by the Patient-Centered Outcomes Research Institute as they are valuable in ensuring basic benchmarks have been met. I recommended four changes to GRADE: (1) the use of appropriate PCORI-endorsed checklists; (2) removal of the de facto hierarchy; (3) clear expectations of study quality, similar to the USPSTF, would be provided for each type of study; and (4) detailed criteria for up and downgrading would need to be provided. I used the GRADE methodology is a good starting point because it is well-accpeted and requires relatively few adaptions to be more applicable to vaccince research.

Chapter Five: Ethics

Influenza vaccine shortages are most commonly caused by manufacturing delays and novel virus strains necessitating a new vaccine to be developed. Target-population recommendations allow those most at-risk for severe outcomes from infection with the influenza virus to receive priority during a vaccine shortage. While the recommendations provide the epidemiological justification for the vaccine's use, the recommendations lack a clearly defined ethical justification. The ethical justification for the target-population recommendations is significant because the target-population recommendations limit access to a potentially lifesaving intervention. This chapter seeks to provide the ethical framework and reasoning in support of the target-population recommendations.

A key presumption of this chapter, and arguably of this project, is that the research on the influenza vaccine and virus has been conducted ethically. The determination of what makes research ethical is beyond the scope of this project, but it is important to note that research to improve the influenza vaccine and understand the influenza virus, although critically important, must rely on ethical conduct. More importantly, society cannot "afford a single miscarriage of justice, a single inequity in the dispensation of its laws, the violation of the rights of even the tiniest minority, because these undermine the moral basis on which society's existence rests."[472] Research must be ethical not simply to fulfill regulatory requirements; research must be ethical because when it is not society loses trust. Trust is lost not only in the research but in the

[472] Hans Jonas, "Philosophical Reflections on Experimenting with Human Subjects" in *Biomedical Ethics and the Law*, eds. James M. Humber and Robert F. Almeder (New York: Springer,1976):217-42.

intervention itself, the policy recommending the intervention, and the entire scientific and medical community. The public needs to not only trust that the vaccine is safe and effective but that the process to determine distribution is fair and just.[473] The goals of vaccination cannot be met if the vaccine, or vaccine policy, is developed with unethical research.

The primary goal of the influenza vaccine is the prevention of severe illness and death.[474] An additional goal of vaccination is the preservation of essential services, such as healthcare, emergency, and public services.[475] Allocation of the influenza vaccine is required to meet these goals during a shortage, as the manufacturing process simply does not allow for rapid production of large qualities of the vaccine. Public statement of goals is important when making difficult choices as the goals can conflict with each other. While healthcare providers and emergency medical services are part of the current target-population recommendation, public services such as sanitation and transit workers are not. In the event of a severe pandemic, policymakers may have to choose between protecting those most at risk and those who provide essential services. I argue that the target-population recommendations for influenza vaccination are fair and equitable despite the shortcomings in the evidence base discussed earlier for three reasons. First,

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[473] P. O'Malley, J. Rainford, and A. Thomoson, "Transparency during Public Health Emergencies: From Rhetoric to Reality" *Bulletin of the World Health Organization* 87 no. 8 (August 2009): 614–18.

[474] World Health Organization, "Influenza Vaccines WHO Position Paper" *Weekly Epidemiological Record* 80, no. 33 (August 19, 2005): 277-88.; Anthony E. Fiore, Timothy M. Uyeki, Karen Broder, et al., "Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010" *Morbidity and Mortality Weekly Report* 59, no. Rr-8 (August 6, 2010): 1-62.

[475] James Hadler, "Public Health Strategies for Distribution of Influenza Vaccine during an Influenza Pandemic" *Yale Journal of Biology and Medicine* 78 (October 2005): 273-82.

the target-population recommendations are based on the best evidence currently available and evolve with changes in the evidence. Second, the target-population recommendations can be supported by the ethical theory of utilitarianism. Finally, the target-population recommendations satisfy the principle of justice.

I believe the target-population recommendations for influenza vaccination are fair and equitable. This belief is supported by the fact that the target-population recommendations are based on the best available clinical evidence and evolve along with changes in that evidence. Logically, this trend will continue and as the evidence improves so will the recommendations. Ideally, the target-population recommendations would be supported with well-powered, rigorously conducted RCTs in all target-populations.[476] Realistically, this is not a possibility due to the ethical and logistical challenges in influenza vaccine research.[477] Vaccination is the standard of care, to design a randomized trial in which the control group did not receive the vaccine would be unethical, especially in high-risk populations. Logistically, influenza vaccine trials are exceedingly difficult to plan because the season is so unpredictable. Additionally, recruiting and completing trials within the influenza season is challenging. The influenza season is relatively short, in the Northern hemisphere, activity begins around October and peaks in January/February, with the exact timing of outbreaks varying by city. The influenza vaccine is not available until the end of August to early September giving a very short recruitment and

[476] As discussed in chapter four, the vast majority of RCTs are completed in healthy patients.
[477] As discussed in chapter one and chapter two.

vaccination time for trials. An additional complication is determining if a particularly high vaccine efficacy rate is due to a very good match or a low virus circulation.[478]

As discussed in chapter four, RCTs, while an excellent source of information, are simply unable to provide the necessary evidence base in target-populations by themselves. Unfortunately, the current research evaluation methodologies prefer RCTs. I state in chapter four that observational trials are more feasible, than RCTs and arguably provide similar evidence. However, observational trials are considered lower quality research, and this contributes to the criticism of the target-population recommendations as weak.[479] Despite the gaps in evidence, target-population recommendations represent the best evidence available, and this evidence has shown that these groups have a higher burden when infected. Additionally, the influenza vaccine has repeatedly been shown to be safe.[480]

The target-population recommendations evolve with changes in the evidence which is one their strengths. The CDC expanded the influenza vaccine recommendations for children as research became available regarding safety, efficacy, and missed influenza

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[478] Robert M. Jacobson, Paul V. Targonski, and Gregory A. Poland, "Why Is Evidence-Based Medicine so Harsh on Vaccines? An Exploration of the Method and Its Natural Biases." *Vaccine* 25, no. 16 SPEC. ISS. (2007): 3165–69. doi:10.1016/j.vaccine.2007.01.049.

[479] Paul E. Alexander, et al., "World Health Organization Strong Recommendations Based on Low-Quality Evidence (Study Quality) Are Frequent and Often Inconsistent with GRADE Guidance" *Journal of Clinical Epidemiology* December 19, 2014. doi:10.1016/j.jclinepi.2014.10.011.

[480] Michael T. Osterholm, Nicholas S. Kelley, Alfred Sommer, and Edward A. Belongia, "Efficacy and Effectiveness of Influenza Vaccines: A Systematic Review and Meta-Analysis" *Lancet Infectious Disease* 12, no. 1 (January 2012): 36-4; Kristen L. Nichol, and John J. Treanor, "Vaccines for Seasonal and Pandemic Influenza" *Journal of Infectious Diseases* 194, Suppl 2 (November 2006): S111-S118.; Tom Jefferson, et. al.,. "Vaccines for Preventing Influenza in Healthy Adults" *Cochrane Database Systematic Reviews* no. 7 (July 2010): CD001269.; Tom Jefferson, et al., "Vaccines for Preventing Influenza in Healthy Children" *Cochrane Database of Systematic Reviews*, no. 2 (April 2008): CD004879.

diagnosis.[481] When the CDC determined that 85 percent of the United States population was recommended to receive the seasonal influenza vaccine the recommendations were updated to include all persons over six months of age without contraindications to avoid confusion about the indications and increase vaccine coverage.[482] Basing recommendation on evidence requires flexibility by the policymakers and for them to stay up to date on the latest information. This flexibility allows for appropriate changes to address new updates; such as the June 2016 announcement that the nasal spray formulation of the influenza vaccine has been shown to be ineffective and thus was not recommended for use in the United States during the 2016-2017 influenza season.[483] This flexibility illustrates the utilization of the best available evidence to support the goals of vaccination.

The remainder of this chapter will address my claim that the current recommendations can be supported on ethical grounds. I will lay the groundwork for how formal ethical theories such as utilitarianism can be utilized to defend allocation decisions that favor one group of individuals over another. I will draw on the work of political philosopher John Rawls to justify my contention that the current

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[481] Scott A. Harper, et al., "Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP)" *Morbidity and Mortality Weekly* 53 RR06 (May 28, 2004): 1–40. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5306a1.htm.; Nicole M. Smith, et al., "Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP)." *Morbidity and Mortality Weekly* 55 RR10 (July 28, 2006): 1–42. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5510a1.htm.; Katherine A. Poehling, et al. "The Underrecognized Burden of Influenza in Young Children." *The New England Journal of Medicine* 355, no. 1 (July 6, 2006): 31–40. doi:10.1056/NEJMoa054869.

[482] Anthony E. Fiore, et al., "Prevention and Control of Influenza with Vaccines." *Morbidity and Mortality Weekly* 59 RR08 (August 6, 2010): 1–62. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5908a1.htm.

[483] Susan Scutti, "CDC Panel Recommends against Using FluMist" *CNN Health*, June 23, 2016. http://www.cnn.com/2016/06/22/health/cdc-flumist-nasal-spray-flu-vaccine/.

recommendations can be defended on the grounds that they are "fair' in terms of their distribution of a needed resource to targeted groups. This analysis is not meant to be a critique of the recommendations per se, but rather to reveal and uncover the moral values at the base of influenza vaccine policy. Thus, my concern is to draw attention to the underlying ethical and moral concerns that are at the heart of these guidelines and to offer a justification for why I believe they are both ethically sound and worthy of our adherence and trust. I begin with a synopsis of classical utilitarianism which is focused on the Greatest Happiness principle, and then discuss pertinent aspects of the concept of Justice as Fairness promulgated by John Rawls. The chapter will conclude with a discussion on the impact of trust and vaccine acceptance.

UTILITARIANISM

Target-population recommendations are supported by the ethical theory of utilitarianism. The theory of utility judges the rightness of actions based on the consequences created with the aim being the creation of pleasure (or avoidance of pain) for the greatest number of people.[484] Vaccines work to benefit society by decreasing the rate of illness and death from diseases. Vaccination supports the greatest good for society by increasing the health and wellbeing of its members. Jeremy Bentham and John Stuart Mill are credited with the classic origins of utilitarianism.[485] I have chosen utilitarianism as a guiding ethical framework because of its frequent application in allocation and triage

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[484] Tom L. Beauchamp and James F. Childress, *Principles of Biomedical Ethics*. 7th Edition (New York: Oxford University Press, 2013) 354.

[485] Jeremy Bentham, "The Utilitarian Calculus," in *Ethical Theory: Classical and Contemporary Readings*, eds. Louis P. Pojman and James Fieser, 6th Edition., (Boston, Wadsworth, 2011):194–96.; John Stuart Mill, *Utilitarianism* (New York: Barnes & Noble, 2005)

frameworks.[486] There are three general public health purposes of vaccination: 1) preservation of life, 2) prevention of infection, and 3) maintenance of public services.[487] The specific goal of the influenza vaccine is to prevent severe illness and death. While vaccinating all persons would provide the best protection, and arguably contribute the most to overall happiness, this is neither realistic nor feasible. Population-wide vaccination is not feasible due to manufacturing capabilities. Additionally, mandatory vaccination would violate the deeply held right to personal autonomy. Allocation plans utilizing the target-population recommendations are required to manage the public health impact of pandemic influenza. Target-population recommendations further the goal of utilitarianism, the greatest good for the greatest number, by increasing the health and wellbeing of both individuals who receive the vaccine and society as a whole by decreasing the rate of infection. This section will briefly introduce allocation decision criteria and then move to a discussion of John Stuart Mill's utilitarianism in relation to the target-population recommendations.

Literature suggests that a moderate to severe pandemic could cost over a million lives in the United States alone.[488] In the event of pandemic influenza, the CDC estimates that less than 10 percent of the US population can be vaccinated with currently manufacturing abilities.[489] It is estimated that with a manufacturing capacity of up to five

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[486] Kennedy, Kathryn. et. al., "Triage: Techniques and Applications in Decision making," *Annals of Emergency Medicine* 28 no. 2 (1996): 136-44.; G. Reay, and J. A. Rankin, "The Application of Theory to Triage Decision-Making," *International Emergency Nurse* 21 no. 2 (April 2013): 97-102.

[487] James Hadler, "Public Health Strategies for Distribution of Influenza Vaccine during an Influenza Pandemic" *Yale Journal of Biology and Medicine* 78 (October 2005): 273-82.

[488] Kristin L. Nichol, John J. Treanor, "Vaccines for Seasonal and Pandemic Influenza " *Journal of Infectious Disease* 194, Suppl 2 (November 1, 2006):S111-S118., S112.

[489] Hadler, 275.

million doses per week, it would take up to two years to produce enough vaccine for the United States population.[490] While the allocation of vaccines is the specific focus of this section, it is also important to note that all healthcare resources could require allocation during an influenza pandemic. Models suggest that a 1918 level pandemic would require 400 percent of current intensive care beds and 200 percent of ventilators which already operate at 90 percent capacity.[491]

The four most commonly suggested criteria in making allocation decisions are broad social value, instrumental value, maximizing life years and the life cycle principle.[492] Broad social value considers the patient's overall worth to society by using the past and future contributions to merit prioritization.[493] Instrumental value weighs the individual's ability to carry out a specific function that is essential to prevent social disintegration or death, giving priority to front line healthcare workers and first responders.[494] Maximizing life years balances medical need with expected survival post-treatment, with the goal to allow the highest number of years to be lived.[495] The life cycle principle prioritizes the young because they have had the least chance to go through life stages.[496] The target-population recommendations embrace the instrumental value (healthcare workers and caregivers), maximizing life years (patients with chronic health

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[490] Hadler, 275.

[491] Ibid.

[492] Douglas White et. al., "Who Should Receive Life Support During a Public Health Emergency? Using Ethical Principles to Improve Allocation Decisions," *Annals of Internal Medicine* 150, no. 2 (January 2009):132-138.

[493] Ibid., 136.

[494] Ibid., 136.

[495] Ibid., 137.

[496] Ibid., 136.

conditions) and the life cycle (children) criteria. Broad social value is not often used because, like any social utility criteria, it is subject to a large fluctuation and subjective criteria. Additionally, I would argue that broad social value gives too many opportunities for discrimination. Allocation via target-population recommendations is not the only option for distributing vaccine supplies. Vaccines can also be distributed via the free market, via government purchase and distribution of the entire stock, and partial purchase and distribution by the government.[497] Free market distribution is not feasible because healthcare is not a free market. Third party payers who have responsibilities to their members dominate the healthcare market in the United States. Additionally, a free market distribution plan would encourage hoarding and create a dangerous black market. During the 2004/2005 vaccine shortage, "two-thirds of respondents believed that wealthy or influential people would be able to get the vaccine even if they were not in a high-risk group" illustrating the need for an ethical allocation process that is enforced fairly.[498] Complete and partial governmental purchase would require allocation decisions to be made. Any allocation policy raises the question of mandatory vaccination. In the United States, the federal government does not have the authority to mandate vaccinations for anyone outside of the military.[499]

Jeremy Bentham was an English philosopher who is regarded as one of the founders of utilitarianism. For Bentham, morally obligatory actions are those which produce the greatest pleasure for the greatest number of people. Bentham's utilitarianism

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[497] Hadler. 275-6.

[498] Catherine M. DesRoches, Robert J. Blendon, and John M. Benson. "American's Responses to the 2004 Influenza Vaccine Shortage." *Health Affairs* 24, no. 5 (May/June 2005): 822-31, 825.

[499] States do have the power to mandate vaccines, as confirmed by the Supreme Court of the United States in *Jacobson v. Massachusetts* 197 U.S. 11 (1905)

was hedonistic in nature, meaning that good actions were equated with pleasure and gratification. Under a hedonistic utility, the fundamental motivation of human life is the pursuit of pleasure and the avoidance of pain.[500] In Bentham's essay "The Utilitarian Calculus" the following four criteria are considered in evaluating pain and pleasure: intensity, duration, certainty/uncertainty, and propinquity/remoteness.[501] An act is additionally considered based upon the chance it will cause sensations of the same kind (fecundity and parity) and the number of people it will impact in the same way.[502] If an action causes more pleasure than pain or avoids pain, then, that action is considered morally good. Under Bentham's utilitarianism, action that will absolutely cause extreme pleasure for even a brief moment at a definitive time point in the very near future will be deemed a morally right action over a potential action which may cause mild pleasure for a longer period of time at an uncertain point in the distant future. Vaccination is a morally good action under Bentham's utilitarianism because the influenza virus can impact a large percentage of the population, causing severe respiratory distress leading to complications including death; avoidance of this pain would be morally good. The target-population recommendations would be considered a morally good act by vaccinating those at most risk of severe illness in order to avoid pain. Even though the target-population recommendation only directly benefits a portion of the population, the indirect

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[500] Henry R. West, *The Blackwell Guide to Mill's Utilitarianism* Blackwell Guides to Great Works (Malden, MA: Wiley-Blackwell, 2006)

[501] Jeremy Bentham, "The Utilitarian Calculus." in *Ethical Theory: Classical and Contemporary Readings*, 6th Edition eds. Louis P. Pojman and James Fieser, 6th Edition, (Boston, MA: Wadsworth, 2011.): 194–96, 195.

[502] Ibid., 195.

benefits of the reduced risk of spreading infection, the physical pain of infection and the emotional pain of losing a loved one, reverberate throughout society.

John Stuart Mill's utilitarianism elaborates the Greatest Happiness Principle. Mill modifies Jeremy Bentham's hedonistic utilitarianism by a substitution of pleasure for happiness.[503] Under the Greatest Happiness Principle actions are judged based on their ability to increase happiness and deflect pain: "Actions are right in proportion as they tend to promote happiness, wrong as they tend to produce the reverse of happiness. By happiness is intended pleasure, and the absence of pain; by unhappiness, pain and the privation of pleasure."[504] The modification of pleasure to happiness appears to be in response to the criticism of Bentham as representing "human nature in a degrading light; since the accusation supposes human beings to be capable of no pleasures except those of which swine are capable."[505] While Mill does not set a specific priority ranking of happiness in his work, he does remark that "utilitarian writers, in general, have placed the superiority of mental over bodily pleasures. . . It is quite compatible with the principles of utility to recognize the fact that some kinds of pleasure are more desirable and more valuable than others."[506] The ultimate end of the Greatest Happiness Principle is to allow an existence:

> exempt as far as possible from pain, and as rich as possible in enjoyments, both in point of quantity and quality, the test of quality and the rule for measuring it against quantity being the pleasure felt by those who, thier

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[503] John Stuart Mill. "Utilitarianism." In *Ethical Theory: Classical and Contemporary Readings* 6th Edition eds. Louis P. Pojman and James Fieser, 6th Edition, (Boston, MA: Wadsworth, 2011.): 197–229, 197.

[504] John Stuart Mill, *Utilitarianism* (New York: Barnes & Noble, 2005):7.

[505] Mill, *Utilitarianism* 8.

[506] Mill, *Utilitarianism* 8.

> opportunists of experience, to which must be added their habits of self-consciousness and self-observation can test furnished with the terms of comparison.[507]

I interpret the Greatest Happiness Principle to support a full life for each member of society as that person defines it.[508] The happiness of individuals contributes to the overall flourishing of society. Influenza vaccination increases the happiness of both the individual and society by preventing the pain of infection with the influenza virus. The target-population recommendations promote the Greatest Happiness Principle by the avoidance of harm in those most at risk, by preventing the spread of disease, while still allowing individual choice by not mandating vaccination. While mandating vaccination would avoid the most harm during a pandemic situation, I would argue that the negation of personal autonomy would violate the Greatest Happiness Principle. Mill states that the "multiplication of happiness is an object of virtue, " but the occasions which an individual is called upon to consider the greater good is limited.[509] Accepting that you as an individual may not be among the target-population recommendations but supporting and complying with the policy is one the few times public utility can be considered. The greater good of society occasionally conflicts with personal liberty and autonomy because the greater good of society requires that the individual gives up something they want or subject themselves to something they would rather not do for the benefit to the aggregate. This is how utilitarianism benefits a functional society, by recognizing we are

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[507] Mill, *Utilitarianism* 12.

[508] Happiness is perhaps the most unhelpful word Mill and Bentham could have chosen. The Greatest Happiness Principles is not tied to emotions. I believe what Mill was suggesting is that the Greatest Happiness contributes to the greatest good for society.

[509] Mill, *Utilitarianism* 19.

interdependent beings and acknowledging that the temporary personal aggravation will have long-term benefits for society as a whole. I would argue and believe that Mill would agree, that the potential consequences of severe illness and death justify the prioritization of the target-populations under utilitarianism.

During a shortage of seasonal influenza vaccine supplies, the current CDC target-population recommendations would be supported by Mill's utilitarianism. The goal of the influenza vaccine the prevention of severe illness and death. As outlined above, this coincides with the Greatest Happiness Principle by avoidance of harm. When the influenza vaccine is scarce due to manufacturing delays, the target-population recommendations of those who would suffer greatly is supported by Greatest Happiness Principle because the prevention of pain is a good action

As discussed earlier, the target-population recommendations evolve with changes in evidence and need. The 2009 H1N1 pandemic led to just five target-populations during the initial launch of the pandemic vaccine. During a particularly severe pandemic, the secondary goal of preserving essential functions for society may become the primary goal. A 1918-level pandemic, as outlined earlier, would greatly strain the healthcare system and put essential service providers (healthcare workers, first responders, etc.) at great risk of contracting influenza, as well as spreading the virus. Vaccinating essential service providers would not only reduce the risk of spreading infection but also ensure that required personnel are available to care for those who fall ill. The Greatest Happiness Principle would support the prioritization of those required for the essential functions (healthcare workers, first responders, etc.) over those at risk for suffering in the event of a pandemic to ensure that all members of society could access required services. The

Greatest Happiness Principle values action that avoids pain, prioritizing providers of essential health services avoids pain on multiple levels. First, it lessens the risk of spreading infection. Second, it ensures that healthcare providers will be available to those who need care. Finally, it provides protection to those at greater risk of exposure. While the temporary prioritization of essential service providers over those at risk of severe illness and death may not occur, in the event it would be required the actions would be supported by Mill's utilitarianism.

While the end goal of utilitarianism is the increased happiness of society, it does not question or promote the equal distribution of happiness. Utilitarianism can inadvertently promote immoral actions.[510] For example, while it has been accepted, and regulated, that research involving animals should limit suffering as much as possible, under utilitarianism the argument could be made that if an individual takes great joy in causing harm to the research animal, then the action is justifiable. Utilitarianism also does not differentiate between moral obligations and supererogatory actions and could be used to support the forceful taking of body parts to save those with higher social utility.[511] Finally, utilitarianism can cause or promote unjust distribution if that distribution is based on aggregate satisfaction. The target-population recommendations could lead to unjust distribution if instead of being used to prevent illness and premature death in those most at risk, they were used to withhold the vaccine from those most at risk under the argument that it would increase happiness to provide protection to those most likely to contribute more to society. The argument could be made that such actions simply balance

[510] Tom L. Beauchamp and James F. Childress, *Principles of Biomedical Ethics* 7th Edition (New York, Oxford University Press, 2013):359.

[511] Ibid., 360.

individual liberty with community interest by preserving the lives of those who provide the most benefit to society; however, this runs afoul of any sense of fairness.

JUSTICE

I believe target-population recommendations are fair and equitable because they satisfy the principle of justice. Justice, at its core, is concerned with fairness. A just policy ensures that no one is unduly burdened nor unduly enriched and at the same time strives to promote equality. Equality can refer to strict equality, equality of outcome, or equality of opportunity.[512] This section will focus on the principle of formal justice and distributive justice.

The principle of formal justice also called the principle of formal equality, requires that equal persons be treated equally. Formal justice requires the "impartial and consistent applications of principles whether or not the principles themselves are just."[513] According to moral theorists Beauchamp and Childress, formal justice is formal because it "identifies no particular respects in which equals out to be treated equally, and provides no criteria for determining whether two or more individuals are in fact equals." By having no other criteria than treating equal parties equally the principle is essentially a

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[512] Strict equality is referring to all parties being treated the same regardless of preexisting circumstances. Equality of outcome is when steps are taken to ensure that all parties are afforded the same ends. Equality of opportunity ensures that all opportunities are open to the public.

[513] Brad W. Hooker, "Justice" In *Cambridge Dictionary of Philosophy*, 2nd ed., ed. Robert Audi (Cambridge, Cambridge University Press, 1999): 456-457. Gale Virtual Reference Library (accessed September 23, 2016). http://go.galegroup.com/ps/i.do?p=GVRL&sw=w&u=txshracd2618&v=2.1&it=r&id=GALE%7CCX3450000830&asid=30b9e6814dbf688db5ad4cb5df809954.

formality.[514] This lack of criteria is a shortcoming as the principle lacks substance.[515] Requiring equals to be treated equally is vague and opens the door to potential discrimination. Target-population recommendations treat all persons who fall under them equally; if a person belongs to a group that is at increased risk for severe infection from the influenza virus, then they would receive priority allocation during a vaccine shortage. If a person is not an increased risk for severe infection from the influenza virus, then they do not receive priority. As of 2010, the CDC recommended seventeen target-populations in the case of a vaccine shortage.[516] A challenge to claiming target-population recommendations promote formal justice is the number of populations considered at risk and the evidence used to support them. It may be difficult to substantiate the claim that all seventeen target-population are at equal risk of severe illness from the influenza virus. The 2009 H1N1 pandemic vaccine recommendations allotted priority to just five populations which is much more realistic view and creates equality between those truly at higher risk.[517]

Distributive justice refers to the "fair, equitable, and appropriate distribution of the benefits and burdens determined by the norms that structure the terms of social

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[514] Tom L. Beauchamp, and James F. Childress, *Principles of Biomedical Ethics*. 7th Edition (New York: Oxford University Press, 2013): 251.

[515] Ibid.

[516] Anthony E. Fiore, Timothy M. Uyeki, Karen Broder, et al., "Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010" *Morbidity and Mortality Weekly Report* 59, no. RR8 (August 6, 2010): 1-62.

[517] National Center for Immunization and Respiratory Diseases, "Use of Influenza A (H1N1) 2009 Monovalent Vaccine." *Morbidity and Mortality Weekly Report* 58, no. RR10 (August 28, 2009): 1–8. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5810a1.htm.

cooperation."[518] Beauchamp and Childress present six abstract principles of distributive justice that are used within various theories of justice that hold each person has the right to 1) rules and actions that maximize social utility; 2) maximum of linearity and property resulting from liberty and fair, free market; 3) principles of fair distribution derived from conceptions of the good developed in moral communities; 4) equal measure of liberty and equal access to the good in life that every rational person desires; 5) the means necessary for the exercise of capabilities essential for a flourishing life; 6) the means necessary for the realization of core dimensions of well-being.[519] Most theories do not use all six principles as to do so would claim that each principle identifies a *prima facia* obligation which is difficult considering some of the principles are in competition.[520] Distributive justice can be found in utilitarian, libertarian, egalitarian, and communitarian theories. I will be focusing on Rawls' principles of justice which are an egalitarian or libertarian theory depending on the application.

I have chosen Rawls' theory of justice because the concept of justice as fairness addresses how decisions should be made in order to ensure that burden and benefits are equitably distributed. Rawls theory is meta-ethical, it does not establish a bright-line of what is and is not ethical but instead, develops a framework for determining what actions are ethical. As society evolves what is considered just also evolves; changes in the determination of justice should also be made based upon changes in evidence and circumstances. Ethical decision making ought to be developed like a scientific subject

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[518] Beauchamp and Childress, *Principles of Biomedical Ethics* 250.
[519] Beauchamp and Childress, *Principles of Biomedical Ethics* 253.
[520] Beauchamp and Childress, *Principles of Biomedical Ethics* 253.

over time-based upon the interactions of theory and observation; Rawls theory allows for this development.[521] Rawls' theory of justice is applicable to evidence-based policymaking in that both require the continual consideration of society's needs and resources to ensure that proper actions are being taken to meet the needs of the people.

Rawls defines the concept of justice as the principles which assign rights and duties, defining the appropriate division of social advantages.[522] The principles of justice are Rawls' basic structure of society, what he imagines an ideal society would accept as the initial terms to form social agreements. The principles of justice aim to create balance within society. Rawls refers to the principles of justice as an abstract form of the social contract. These hypothetical principles provide the basis for all future agreements by specifying the acceptable kinds of social cooperation and forms of government to be established.

Rawls' method of reasoning the original position. The original position is a purely theoretical decision-making model that places participants under a veil of ignorance-meaning that they only have access to specific pieces of information. The aim of the original position is to rule out the principles that would only be rational to propose if one knew certain things that are irrelevant from the standpoint of justice.[523] Rawls excludes any information from entering the veil of ignorance that would allow participants to make decisions based on existing prejudices.[524] The original position models fair conditions and acceptable restrictions on the reasons, "under which the representatives of citizens,

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[521] Thomas Nagel, "Rawls on Justice." *Philosophical Review* 82, no. 2 (April 1973): 220-34.
[522] John Rawls. *Theory of Justice*. Revised ed. Cambridge MA: Belknap Press, 1999, 9.
[523] Rawls. *Theory of Justice*. 17.
[524] Ibid.

viewed solely as free and equal persons, are to agree to the fair terms of social cooperation (as expressed by the principles of justice) whereby the basic structure is to be regulated."[525] Parties within the original position are presumed to be rational and mutually disinterested, meaning that they are willing to take the most effective means available to reach a given goal. Rawls assumes that the rational persons do not suffer from envy because envy tends to leave everyone worse off, lack of envy gives men a secure sense of their worth.[526] The purpose of these conditions is to represent equality between human beings as moral persons, as creatures having a conception of their good and capable of a sense of justice.[527]

The process of determining the original position is the reflective equilibrium. The reflective equilibrium is described by Rawls as, "an equilibrium because at last our principles and judgments coincide; and it is reflective since we know what principles our judgments conform and the premises of their derivation. "[528] I imagine this process to be hermeneutical in nature; a give and take of ideas until an agreement is reached. The reflective equilibrium is "reached after a person has weighed various proposed conceptions and he has either revised his judgments to accord with one of them or held fast to his initial convictions (and the corresponding conception)."[529] By utilizing the reflective equilibrium within the original position, the principles of justice can be

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[525] John Rawls, *Justice as Fairness: A Restatement* 2nd ed. Cambridge MA: Belknap Press, 2001, 81.

[526] Rawls, *Theory of Justice*, 124.

[527] Rawls, *Theory of Justice,* 17.

[528] Rawls, *Theory of Justice,* 18.

[529] Rawls, *Theory of Justice,* 43.

determined. The principles of justice are theoretical and therefore can be determined for any set of circumstances.

Rawls holds that there are two provisional principles of justice he believes would be agreed to within the original position:

> (1) Each person has the same indefeasible claim to a fully adequate scheme of equal basic liberties, which scheme is compatible with the same scheme of liberties for all; and
>
> (2) Social and economic inequalities are to satisfy two conditions: first, they are to be attached to offices and positions open to all under conditions of fair opportunity; and second they are to be the greatest benefit of the least-advantaged members of society (the difference principle).[530]

The liberties protected by the first principle include free speech, assembly, conscience and thoughts; and embrace the political rights also protected by the Bill of Rights in the United States. The second principle applies to the distribution of income and wealth, specifically requiring that offices and positions be open to all under the principle of fair opportunity (meaning all who apply themselves have an equal chance).[531] The Difference Principle seeks to find a balance between those who are enriched by their circumstances and those who are burdened by them; any inequality in distribution must be for the benefit of those less advantaged. In *Justice as Fairness: A Restatement,* Rawls clarified that the difference principle applies only to existing inequalities, not those created by hard work and effort.[532] These initial principles of justice are meant to deal

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[530] Rawls, *Justice as Fairness: A Restatement,* 42-43.

[531] Rawls, *Theory of Justice*, 43

[532] "However great the inequalities in wealth and income may be and however willing people are to work and earn their greater shares of output, existing inequalities must contribute effectively to the benefit of the least advantage." Rawls. *Justice as Fairness: A Restatement* 64.

with what Rawls refers to as the primary goods. Primary goods are things that every rational person is presumed to want; these goods are divided into social and natural goods.[533] Social goods include rights, liberties, opportunities, wealth, and self-respect. Natural goods include health, vigor, intelligence, imagination; however, they are not directly controlled. Therefore, the question regarding target-population recommendation for influenza vaccines becomes two-fold. First, do the principles of justice apply to the target-population recommendations? Second, are the target-populations less advantaged? I argue in the affirmative to both below.

Vaccine distribution falls under the primary, natural good of health and thus applies to Rawls' initial principles of justice.[534] Primary goods are presumed to be desired by all people; however, natural goods are not directly controlled. The government cannot allocate good health to its citizens, but it can provide access to resources and services to improve health. Access to those services and resources should ideally be equal in a just society. As established in chapter one, the influenza vaccine has been proven to be safe and effective in reducing influenza infections and the resulting complications. Therefore, the principles of justice apply to target-population recommendations.

The difference principle has mainly economic application, and thus the application to healthcare may appear unclear or an overextension of the theory.Rawls meant for the difference principle to protect those less advantaged from becoming further disadvantaged. In a theoretically equal society, all members would have an equal risk of

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[533] Rawls, *Theory of Justice*, 54.

[534] Ibid. Primary goods are divided into national and social goods; natural goods included health, vigor, intelligence and imagination.

contracting influenza and equal access to the influenza vaccine. In a theoretical society, a different allocation method would be used. In our current society, target-populations have an increased risk of influenza infection and resulting complications that are not the result of individual effort.[535] The influenza virus impacts the human population disproportionally, those with existing health conditions face higher risks and burdens than those who are in better health. Members of the target-populations are less advantaged members of society. As justice requires the fair distribution of risks and burdens, justice demands that those who are at an increased risk of severe infection and premature death due to the influenza virus receive priority access to the vaccine during a vaccine shortage.

Pandemic Application

Target-population recommendation may not always prioritize those at most risk from severe illness. Although historically the CDC has chosen to prioritize at-risk populations there is a possibility that given a large scale pandemic that the CDC would be forced to prioritize essential service providers. The 2009 H1N1 pandemic vaccine recommendations prioritized healthcare workers and emergency services personnel in addition to those experiencing high rates of infection not only because they are at greater risk for exposure but because they perform essential public health functions. While ideally, even limited vaccine supplies would be sufficient to allow vaccination of essential service personnel and those at high risk of severe illness; in the event of a 1918 level pandemic vaccinating essential service providers to reduce transmission and preserve required services would be supported by the principle of justice. Prioritizing

[535] The argument could be made that certain members of the target-populations have control over their health status, particularly those with diabetes and other chronic conditions, however this argument is well beyond the scope of this project.

health care providers and other essential personnel would be considered just under the principle of formal justice. Essential personnel would be defined as equal, and that definition can be consistently and impartially applied. Rawls requires that any inequalities in distribution be to the betterment of those least advantaged. The argument could be made that by nature of their professions, healthcare workers, and other essential service providers are less advantaged because they are at higher risk. However, this does not invoke the difference principle because they have been disadvantaged by their individual actions. While I strongly disagree with the idea that those who chose to put their lives in danger would be provided with less protection because of their chosen profession. I support Rawls limitation of the difference principle; I believe that the prioritization of healthcare workers and first responders would be accepted within the original position. In the original position, as discussed above, the parties are rational and mutually disinterested, willing to reach a compromise for common goals. In this case, the common goal would be the continuing essential services through a pandemic. I believe that the temporary prioritization of healthcare workers and other essential service continue the availability of required services would be accepted within the original position. Although a theoretical decision-making model, the original position allows for the consideration of ideas from a non-prejudicial standpoint to determine the fair distribution of goods. I believe that the prioritization of healthcare workers and first responders would be accepted within the original position because the prioritization would be temporary, would be done to preserve essential public health services, and only used in the event of a pandemic influenza causing a severe shortage that did not allow for the use of target-populations that included those most at risk for severe illness.

The target-population recommendations satisfy the principles of justice by having clear designations that can be consistently applied to balance the risks of influenza infections within society. The use of target-populations to allocate the influenza vaccine are fair and equitable, even though the recommedations have changed over time, and could drastically change in the event of a severe pandemic. Where both Mill and Rawls potentially suffer is arguing against the principle of liberty. Personal liberty is a closely and passionately protected right, "your freedom ends at the start of my nose." Liberty, including autonomy, is why compelled vaccination will not work in the United States, vaccination must be a personal choice. The requirement for personal choice is why the evidence base for the recommendation and the way that the evidence and recommendations are communicated are so important.

TRUST

Polices with a solid ethical foundation can increase public trust, and therefore compliance. Trust is a key component of public health policy:

> The reality is that most measures for managing public health emergencies rely on public compliance for effectiveness. Measures ranging from hand washing to quarantine require public acceptance of their efficacy, as well as acceptance of the ethical rationale for cooperating with instructions that may limit individual liberty so as to protect the broader public from harm.[536]

Target-population recommendations rely upon public compliance to be effective. Vaccines can only be effective if they are administered. Public compliance is dependent on trust in the vaccine, in the decision (including the decision maker and the process) and

[536] P. O'Malley, J. Rainford, A. Thomoson. "Transparency during Public Health Emergencies: From Rhetoric to Reality" *Bulletin of the World Health Organization* 87 no 8 (August 2009):614-618, 616.

the ethical justification.[537] Trust is the belief in the reliability, truth, ability or strength of an entity, person, or intervention.[538] For the target-population recommendations asking the public to trust, and comply with, the recommendation is actually asking the public to believe that the research to create the vaccines has been conducted accurately, and ethically. To trust the correct virus strains for inclusion in the vaccine were chosen. To trust the vaccine was manufactured correctly and safely; meaning that the manufacturer, the distributor and all of the various employees are trustworthy. Finally, by asking the public to trust the target-population recommendation, we are asking them to trust that the policy is accurate, ethical, and free of bias and conflicts of interest. Asking for the public to trust all of this is no simple thing, especially in light of past ethical missteps. Ethics and trust go hand-in-hand, once trust is invoked, an obligation to act ethically is also created.[539] There are three main trends that have contributed to the distrust of vaccines. First is the increasing challenge to scientific evidence.[540] Second, distrust of the pharmaceutical industry's influence on policy and the agenda of government sponsored science.[541] Finally, a general mistrust of biomedical research and government health

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[537] Ibid.

[538] *Merriam Webster Dictionary*. s.v. "Truth" Accessed September 30, 2016, https://www.merriam-webster.com/dictionary/truth

[539] Susan Dorr Goold. "Trust and the Ethics of Health Care Institutions." *The Hastings Center Report* 31, no. 6 (November 2001): 26. doi:10.2307/3527779.

[540] Leonard Ortmann, and John Iskander, "The Role of Public Health Ethics in Vaccine Decision Making: Insights from the Centers for Disease Control and Prevention" In *Vaccinophobia and Vaccine Controversies of the 21st Century*, 291–305, 292. New York, NY: Springer New York, 2013. doi:10.1007/978-1-4614-7438-8_15.

[541] Ibid.

programs due to the disclosure of serious abuses.[542] This distrust contributes to vaccine hesitancy.

The WHO defines vaccine hesitancy as a "delay in acceptance or refusal of vaccines despite the availability of vaccination services."[543] Vaccine hesitancy is caused by a number of factors. First is the success of vaccines themselves. Vaccines have controlled many once common childhood illnesses. Thus the fear has shifted from the vaccine-preventable disease to the vaccine itself.[544] Many parents do not remember polio, measles, or even severe outbreaks of influenza. High disease rates and burdens create public support for vaccination programs. As the vaccine is effective, disease rates decrease, and the memory of the disease fades.[545] Eventually, any adverse event related to vaccination becomes more common than the disease itself and therefore as unacceptable as the disease once was.[546] Although heart attacks, strokes, miscarriages, and seizures occur daily, if an incident happens to occur around the same time as vaccination, the vaccination will often be blamed.[547] This is the nature of the anti-vaccination narrative; despite robust evidence that says the influenza vaccine is safe, the personal narrative of an injured party will always be stronger and add to vaccine hesitancy. The CDC has begun to include narratives of families who suffered the effects of vaccine-preventable diseases on their website to illustrate the dangerous of not vaccinating but the impact of

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[542] Ibid.

[543] Daniel A. Salmon, et al.,"Vaccine Hesitancy: Causes, Consequences, and a Call to Action" *American Journal of Preventive Medicine* 49, no. 6 Suppl 4 (December 2015): S391-8, S391. doi:10.1016/j.amepre.2015.06.009.

[544] Ibid., S392.

[545] Ortmann and Iskander. "The Role of Public Health Ethics in Vaccine Decision Making." 293.

[546] Ibid.

[547] Donald G. McNeil Jr. "Don't Blame Flu Shots for All Ills, Officials Say." *The New York Times*, September 29, 2009. www.nytimes.com/2009/09/28/health/policy/28vaccine.html?_r=0.

these narratives is unclear.[548] The mandatory nature of vaccination for school entry in many states adds to vaccine hesitancy because it removes autonomy from parents.[549] Perhaps the number one reason for vaccine hesitancy is a lack of trust in manufacturers, the government, and physicians who recommend vaccines.[550] Stark policies and straight data will never compete with the personal narratives of vaccines injuries, but I believe the combination of a solid ethical framework with a compelling rhetorical argument that promotes transparency and trust will aid the vaccination effort. In order for the target-population recommendations to be accepted by the public, the public must trust the decision-making process, including the ethical foundation of that process.[551] This section will discuss the importance of trust in public health policy using the H1N1 pandemic as an example.

A substantial number of people refused the H1N1 pandemic vaccine because they did not believe influenza infection posed a serious health risk and they had concerns over vaccine safety.[552] The same study cited disapproval with the vaccine shortage itself and how the government handled allocation.[553] The distribution of the H1N1 pandemic vaccine was over promised and under delivered. On October 24, 2009, *The New York Times* reported that 16 million doses of the vaccine were available, with 30 million

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[548] Centers for Disease Control and Prevention. "Vaccines: VPD-VAC/Unprotected-Stories." Accessed October 3, 2016. http://www.cdc.gov/vaccines/vpd-vac/unprotected-stories.htm.

[549] Vaccination exemptions do exist in many areas but are not applied universally. Salmon, et al. "Vaccine Hesitancy." S394.

[550] Salmon, et al. "Vaccine Hesitancy." S396

[551] P. O'Malley, J. Rainford, A. Thomoson. "Transparency during Public Health Emergencies: From Rhetoric to Reality" *Bulletin of the World Health Organization* 87 no 8 (August 2009):614-618.

[552] Gillian K. SteelFisher, et al., "The Public's Response to the 2009 H1N1 Influenza Pandemic" *New England Journal of Medicine* 362, no. 22 (June 3, 2010): e65, e65(5). doi:10.1056/NEJMp1005102.

[553] Ibid.

projected to be available by the end of the month.[554] With the pandemic starting in April 2009, this seems impressive, until you take into account that the government had planned, and announced, that 120 million doses would have been available by the end of October.[555] Clinics were planned, and announced, but could not be opened due to the lack of vaccine supply.[556] In Chicago, there were reports of people lining up two hours before the clinic was slated to open only to be turned away.[557] One woman, who was nine months pregnant stated, "You hear it's a national emergency, and it scares you."[558] This statement highlights the lack of communication regarding the situation. President Obama had declared a national emergency, but not because the H1N1 was particularly lethal or the vaccine was especially scarce; the declaration of the national emergency allowed hospitals to set up vaccination clinics outside of normal geographic areas.[559] One woman in Centreville, Virginia admitted to lying to the administering doctors about being pregnant to receive the vaccine stating "I'm religious. I don't lie. But it's not about me. It's for my son. It's safer for him if I have the antibodies", her 11-week-old son a could not yet be vaccinated against influenza.[560] Despite this urgency during the shortage, once the vaccine was readily available the same patients who clamored for the vaccine were

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[554] Donald G. McNeil Jr., "Don't Blame Flu Shots for All Ills, Officials Say." *The New York Times*, September 29, 2009. www.nytimes.com/2009/09/28/health/policy/28vaccine.html?_r=0.

[555] Jackie Calmes, and Donald G. McNeil Jr., "H1N1 Widespread in 46 States as Vaccines Lag." *The New York Times*. October 24, 2009. http://www.nytimes.com/2009/10/25/us/politics/25flu.html?_r=0.

[556] Ibid.

[557] Ibid.

[558] Donald G. McNeil Jr., "Don't Blame Flu Shots for All Ills, Officials Say" *The New York Times* September 29, 2009. www.nytimes.com/2009/09/28/health/policy/28vaccine.html?_r=0.

[559] Jackie Calmes, Donald G. McNeil Jr., "H1N1 Widespread in 46 States as Vaccines Lag" *The New York Times*. October 24, 2009. http://www.nytimes.com/2009/10/25/us/politics/25flu.html?_r=0.

[560] Donald G. McNeil Jr., "Don't Blame Flu Shots for All Ills, Officials Say" *The New York Times*, September 29, 2009. www.nytimes.com/2009/09/28/health/policy/28vaccine.html?_r=0.

hesitant to receive it, "But my formerly desperate patients are now leery. 'It's not tested,' they said, 'Everyone knows there are problems with the vaccine. I'm not putting that in my body.'"[561] It was not that the pandemic didn't happen, but that the pandemic virus did not cause as serious an illness as people assumed that it would; the risks of contracting H1N1 did not outweigh the imagined risks of the vaccine. While many people became ill with H1N1, the pandemic virus did not have a very high mortality rate. For these reasons, the public did not trust the government, the doctors, or the manufacturers that the vaccine was necessary.

Trust requires open, honest communication about what is both known and unknown.[562] Trust is particularly important in healthcare due to the patient's vulnerable position in comparison to that of the healthcare provider and vaccine manufacturer. In a pandemic, individual patients also have very little control over the situation. Knowledge is gained through the observation of action, highlighting the importance of transparency.[563] Behavior that is predictable or reliable encourages trust even if that behavior is unfavorable.[564] For example, a physician who is consistently fifteen to thirty minutes behind schedule will likely not face as much criticism from their patients as a physician who varies widely in their schedule. Actions of beneficence, advocacy, competence, and fairness bolster trust as does time and experience.[565] Repudiation

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[561] Danielle Ofri, "The Emotional Epidemiology of H1N1 Influenza Vaccination" *New England Journal of Medicine* 361, no. 27 (December 31, 2009): 2594–95, 2594. doi:10.1056/NEJMp0911047.

[562] P. O'Malley, J. Rainford, A. Thomoson. "Transparency during Public Health Emergencies: From Rhetoric to Reality." *Bulletin of the World Health Organization* 87 no 8August 2009): 614–18.

[563] Susan Dorr Goold, "Trust and the Ethics of Health Care Institutions" *The Hastings Center Report* 31, no. 6 (November 2001): 26-33, 30. doi:10.2307/3527779

[564] Ibid.

[565] Ibid.

reinforces distrust, which is why the anti-vaccination movement is so strong. Trust, especially in institutions, is more easily lost than gained, "Betrayal undermines trust out of proportion to its frequency or effect on outcomes" because it causes people to question their abilities to judge others.[566] Parents of children they believe been injured by vaccines often speak of betrayal, their narratives of being betrayed by doctors, the government, vaccine manufacturers, destroys trust faster than it can be built. Increasing the level of the public's trust in vaccines themselves and the target-population recommendations is a high bar. As I recommended in chapter two, this would require the use of the rhetorician' skill set to help parse out the arguments needed to counter the anti-vaccine narrative. The rhetorician would have to be someone would appeal to parents but also be able to interpret complex scientific data and interact with policymakers.

A fair, transparent process for decision-making is key, especially when allocation of limited resources is being determined.[567] In policy, trust is fostered through transparent decision-making. Transparency in policy making must be framed as both a practice and a desired communication outcome. Limits to transparency should be articulated within the policy. For example, within the context of influenza pandemic policies communication should include the process used to develop the target-population recommendation, the members of the panel, and the evidence used. The limits of transparency within the pandemic situation would include inconclusive or incomplete information, information that jeopardizes security, information that leads to discrimination or stigma of a particular

[566] Ibid.
[567] Ibid.

group, or information that leads to harmful behaviors.[568] Information must be provided in a clear, concise manner that is appropriate for the audience.

Public panic can be just as detrimental as a lethal virus. One of the areas in which the H1N1 pandemic response could have been most improved was public communication regarding vaccine availability.[569] The Department of Health and Human Service (DHHS) published the *2009 H1N1 Influenza Improvement Plan* in May 2012, highlighting the need for predetermined communication plans.[570] Specifically, the DHHS noted that communications were not written in lay language and were not adequately distributed to all populations. The DHSS recommends implementing multiple communication partnerships to ensure that information is both understandable and accessible to all people. Fulfilling this recommendation is best done with a policy that embraces evidence-based practice with a strong ethical framework that has been communicated to the public using the rhetorician's skill set. I image this communication plan to have two segments. The first would occur pre-pandemic as a manner of increasing yearly influenza vaccination rates and addressing the concerns of the public on the seasonal vaccine. This would involve engaging in dialogue with vaccine skeptics and anti-vaccine activists as well as providing information regarding influenza infection in a clear, understandable manner. Social media would be better utilized. Public discourse would be encouraged. During the second segment, the need for social distancing during a pandemic prior to

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[568] P. O'Malley, J. Rainford, A. Thomoson, "Transparency during Public Health Emergencies: From Rhetoric to Reality" *Bulletin of the World Health Organization* 87 no. 8 (August 2009): 614–18.

[569] Donald G. McNeil Jr., "U.S. Reaction to Swine Flu; Apt and Lucky." *The New York Times*. January 1, 2010. http://www.nytimes.com/2010/01/02/health/02flu.html.

[570] Kathleen Sebelius, 2012. 2009 H1N1 Influenza Improvement Plan edited by Department of Health and Human Services: US Department of Health and Human Services, 30.

vaccine availability would be made along with accurate (but low) projections of availability and justification for target-populations. Once the vaccine was available, the target-population recommendations would be continuously reinforced and updated as appropriate.

CONCLUSION

This chapter provided my rationale for determining the current target-population recommendation to be fair and equitable as well as a discussion regarding the importance of improving public trust. I argued the target-population recommendations are fair and equitable for three reasons. First, the target-population recommendations are based on the best available clinical evidence and continue to evolve with changes to that evidence. Second, the target-population recommendations are supported by the ethical theory of utilitarianism. The basic theory of utility judges actions based upon their consequences invoking the greatest good for the greatest number. I drew upon Jeremy Bentham's Utilitarian' Calculus and John Stuart Mill's Greatest Happiness Principle to support the target-population recommendations finding that vaccination is a moral good, the target-populations are a moral good because vaccinating those at most risk avoid the physical pain of infection for the target-populations which also reducing the risk of infection and risk of emotional pain of losing a loved one throughout society. Finally, the target-population recommendations satisfy the principle of justice. The principle of justice requires a fair distribution of risks and rewards. I used the principle of formal justice and distributive justice for the basis of this argument. The target-population recommendations satisfy the principle of formal justice by defining the group to be treated equally (those at greater risk of severe illness from influenza infection) and providing criteria that can be

impartially and consistently applied. I used John Rawls' principles of justice as the distributive justice theory, arguing that the target-population recommendations invoke the difference principle due to the uneven risk of infection and severe illness due to influenza in these groups. Justice demands that risk and rewards be fairly distributed; as the influenza virus disproportionally impacts the human population, the influenza vaccine must be allocated in proportion to that risk during times of shortage. Liberty can be used to challenge both the principle of justice and utility. The rights of many are argued to end at the rights of the individual. While the argument for the target-population recommendations is well supported with both justice and utility; the liberty argument, both as a positive liberty for all to receive equal access to the vaccination and a negative liberty to remain unvaccinated will always be a powerful counterargument. At the end of the day, vaccination must be a choice, and that choice requires public trust.

I argued in this chapter that asking the public to trust vaccines is a tall, but not unreasonable, request if research and policy are well communicated. The rhetorician's skill set discussed in chapter two is a vital tool in this endeavor. The rhetorician must be able to counter the anti-vaccine and vaccine skeptic narrative in a respectful manner by embodying pathos and ethos and composing a rational, logical, evidence-based argument that is audience appropriate. Increasing trust in vaccine and vaccine policy will increase vaccination rates.

The target-population recommendations provide the epidemiological rationale for their use, albeit unclearly for the lay population. One area in which the target-population recommendation can improve is providing a clear ethical framework. Target-population recommendations, like most public health regulations, rely on voluntary compliance for

success; having a clear ethical foundation will impact public trust.[571] Trust supports compliance; ethical frameworks support trust. Ethical, trustworthy research and policy that is well-communicated to the public will lead to increased vaccination rates which in turn reduce the public health and socioeconomic burden of the influenza virus.

[571] P. O'Malley, J. Rainford, A. Thomoson, "Transparency during Public Health Emergencies: From Rhetoric to Reality" *Bulletin of the World Health Organization* 87 no. 8 (August 2009): 614–18

Chapter Six: Concluding Remarks

My goal for this project was to propose improvemens to influenza vaccine policy in order to increase vaccination rates, thus reducing the public health burden of the influenza virus. Improvements to influenza vaccine policy are required because despite the general availability of the vaccine only 43.6% of adults and 59.3% of children received the influenza vaccine during the 2014-2015 influenza season.[572] On a yearly basis infection with the influenza virus results in approximately 114,000 hospitalizations.[573] During the 2009 pandemic patients initially clamored for a vaccine then demurred, citing safety concerns.[574] The influenza vaccine has a public relations problem; my proposals will assisting in addressing the misconceptions and misinformation regarding the influenza virus and vaccine leading to increased vaccination rates and reduction of the public health and socioeconomic burdens of influenza infection.

My proposals involve changes to the research evaluation methodology and communication between researchers, the public, and policymakers. The proposals were based on the evaluation of the target-population recommendations through the lenses of history, policy, ethics, and clinical research. Influenza virus epidemiology was provided in chapter one including a historical overview of the pandemics of 1918, 1957, 1968, and

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[572] Centers for Disease Control and Prevention. "Flu Vaccination Coverage United States, 2014-15 Influenza Season," 2014. https://www.cdc.gov/flu/pdf/fluvaxview/nfid-coverage-2014-15-final.pdf

[573] Centers for Disease Control and Prevention, "Seasonal Influenza-Associated Hospitalizations in the United States" http://www.cdc.gov/flu/about/qa/hospital.htm.

[574] Danielle Ofri. "The Emotional Epidemiology of H1N1 Influenza Vaccination." *New England Journal of Medicine* 361, no. 27 (December 31, 2009): 2594–95. doi:10.1056/NEJMp0911047.

2009 to illustrate the impact of influenza even as modern vaccination and antivirals became available. The influenza manufacturing process, and how it necessitates target-population recommendations as part of the plan for shortages was also explained in chapter one. Chapter two discussed the policymaking process and how to leverage classical rhetoric in the quest to improve evidence-based policymaking. In chapter three, I analyzed the target-populations recommendations from both the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) and the processes used to determine the target-population recommendations. Chapter four explored the types of research used to determine the target-population recommendations and the methods for evaluating that research. The ethical framework for the target-population recommendations was developed in chapter five. This final chapter will provide a summary of the project by highlighting the completion of the aims and exploring future directions.

COMPLETION OF AIMS

This project utilized the lenses of science, history, ethics, and policy to evaluate the research that informs the target-population recommendations for influenza vaccination and proposes improvements. These proposals were developed through the completion of the following three aims.

Aim one was the analysis of the current research evaluation methodologies to assess the application to the evidence base for target-population recommendations. This aim required the additional analysis of the types of research used to support the target-population recommendations. This analysis was completed because RCTs are the gold standard in clinical research and as such, most research evaluation methodologies prefer

RCTs to other research types. The research used to support the target-population recommendations was analyzed in two ways, a systematic review of available randomized controlled trials (RCTs) and a categorization of the sources used by the CDC. The systematic review was used to determine if available RCTs could provide an adequate evidence base for the target-population recommendations. Chapter four provides the detailed results of this review. While well-designed, adequately powered, RCTs would ideally be available for all populations; my review revealed most of the influenza vaccine RCTs had been completed using healthy participants.

Table 3: Participant Populations in Randomized Controlled Trials for Influenza Efficacy

Population	**Number of Studies**
Healthcare Workers	3
Families	4
Children with Chronic Disease	2
Adults with Chronic Disease	4
Elderly with Chronic Disease	1
Elderly	5
Pregnant Women	1
Healthy Adults	17
Healthy Children	18
Healthy Adults and Children	3
Not Reported	1

Source: Systematic Review, chapter four

The target-populations are not well represented in RCTs. Given the challenges in vaccine research including time, resources, and the ethical implications of withholding the standard of care, this result is unsurprising. RCTs alone are unable to provide a comprehensive evidence base for the target-population recommendations because studies simply do not exist in all populations. Arguably, RCTs cannot be completed in all of the

target-populations. The CDC recommended seventeen target-populations in the event of a vaccine shortage as of 2010[575]:

1. all children aged 6 months--4 years (59 months);
2. all persons aged ≥50 years;
3. adults and children who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurological, blood, or metabolic disorders;
4. persons who have immunosuppression;
5. women who are or will be pregnant during the influenza season;
6. children and adolescents (aged 6 months--18 years) who are receiving long-term aspirin therapy and who might be at risk for experiencing Reye syndrome after influenza virus infection;
7. residents of nursing homes and other long-term--care facilities;
8. American Indians/Alaska Natives;
9. persons who are morbidly obese (BMI ≥40);
10. health care personnel;
11. household contacts and caregivers of children aged <5 years and adults aged ≥50 years, with particular emphasis on vaccinating contacts of children aged <6 months; and
12. household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza.

Supporting the target-populations with RCTs would be a resource intensive undertaking that may not be feasible. Experts argue that well-designed observational trials may provide as valuable, and potentially more accurate, information than RCTs in regards to vaccine efficacy.[576] These results added to my belief that the research evaluation methodology used to assess influenza vaccine search must be capable of a balanced evaluation of all research types in order to provide a comprehensive research strategy.

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[575] Anthony E. Fiore, et al. "Prevention and Control of Influenza with Vaccines," *Morbidity and Mortality Weekly* 59 RR08 (August 6, 2010): 1–62. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5908a1.htm.

[576] Robert M. Jacobson, Pauk V. Targonski, and Gregory A. Poland. "Why Is Evidence-Based Medicine So Harsh on Vaccines? An Exploration of the Method and Its Natural Biases." *Vaccine* 25, no. 16 (April 20, 2007): 3165-3169.

My systematic review also analyzed the clinical endpoints of the studies to determine if meaningful public health outcomes were being measured. The review showed that severe illness, defined in the review as hospitalization or death, was only measured as a primary endpoint in one study and as a secondary endpoint in four additional studies. The implication of this finding is that researchers may not be looking for influenza in severely ill patients or may not be immunizing those most at risk. The lack of severe illness as a study endpoint in RCTs highlights the need for utilizing all types of research in determining the target-population recommendations and the need for balanced evidence evaluation methodology.

My second analysis for this aim was to determine the types of evidence used by the CDC to determine the seasonal influenza recommendations in the United States. The purpose of this analysis was to provide an example of what research types were being utilized for the target-population recommendations and were required to be evaluated. The research types were obtained by reviewing the citations provided by the ACIP in the recommendations. The sources were obtained and study type determined based on a review of the title, abstract, and article. This analysis was completed to determine the type of research, in addition to the RCT, being used as a basis for the target-population recommendations. The CDC uses a wide breadth of research types to determine the target-population recommendations. In 2005, the following sources were used [577]:

[577] Scott A. Harper, et al., "Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP)," *Morbidity and Mortality Weekly* 54 Early Release (July 13,2005): 1–40. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr54e713a1.htm.

51 RCTs
31 Basic Science Studies
28 Government Reports
22 Observational Therapy Studies
21 Case Reports
12 Reviews
14 Surveillance Studies
3 Editorials
4 Non-clinical manuscripts

The results of the systematic review and the CDC source analysis have highlighted the need for an evidence evaluation methodology that is capable of providing an accurate and balanced assessment of all types of research.

Research evaluation methodologies are used as a part of the peer review process and to rate the quality of recommendations. The preference of RCTs in research evaluation methodologies is a recurring point of discussion throughout chapter four. RCTs are considered the gold standard because of their value in evaluating interventions. However, RCTs cannot provide the complete evidence base for target-population recommendations due to the logistical and ethical barriers to their completion in vaccine research. I analyzed four methods for evaluating research: United States Preventative Service Task Force, the Rules of Evidence on the Use of Antithrombotic Agents, the Oxford Centre of Evidence-Based Medicine's Evidence Levels, and Grading of Recommendations Assessment, Development and Evaluation (GRADE). I also discussed the value of using checklists as a basic guideline in evaluating research. While checklists are not designed to evaluate research, I believe they are valuable to ensure that basic benchmarks have been met. Current research evaluation methodologies are inadequate for considering all these research types because of their two main limitations: inflexibility and preference toward RCTs. Methodologies are based upon a standard hierarchy which places RCTs ahead of other research types. While I am in no way stating that RCTS are

not valuable in vaccine research being able to assess research based on the quality of that particular research type is necessary for a balanced evaluation of vaccine research.

Table 5: Research Evaluation Methodology Summary

USPSTF	**Rules of Evidence**	**Oxford**	**GRADE***
Tier 1- RCTs, Systematic Reviews, Meta-analysis of homogeneous RCTs	Level 1- High powered RCTs	Level 1- Systematic Reviews	High- Randomized
Tier 2- Well-designed controlled trials without randomization	Level 2- Low powered RCTs	Level 2- RCTs or well-designed observational studies	Moderate
Tier 3- Well-designed cohort or case controlled	Level 3- Nonrandomized concurrent cohort	Level 3- Non-randomized trials	Low- Observational
Tier 4- Observational studies with large effects of magnitude	Level 4- Case Series	Level 4- Case-Control studies	Very Low

* The GRADE methodology did allow for studies to be upgraded for large effect, dose response and control for confounding and downgraded based on risks of bias, inconsistency, indirectness.

The methodologies, particularly USPSTF and GRADE, require that the research also be evaluated against study- specific criteria to determine quality within the hierarchy, but there is a preference for RCTs. While an observational study may be an exceptional observational study, it will not be rated as highly as an RCT, with the exception of the Oxford Levels of Evidence. The research evaluation methodologies are discussed in depth in chapter four. Evaluation of research prior to its utilization in the development of policy is required because the use of flawed research could result in flawed, or even harmful, policies. Each of the evaluation methodologies reviewed within this project have valuable aspects; however, none of them are ideal for evaluating vaccine research.

Aim two was the development of recommendations to improve evidence-based policymaking for influenza vaccine policy. This aim required the evaluation of general policymaking procedures in comparison to the evidence-based policymaking process. I advocate for an evidence-based process because of its potential to incorporate high-quality research with policy and citizen involvement. In chapter two, I identified ways that research can be used in policymaking: identifying and clarifying problems, determining the scope of suspected problems, and evaluating policy solutions. The combination of science, policy, and communication can address public concerns about safety and efficacy to increase vaccination rates. Evidence-based policymaking is not simply the insertion of selected research to back up claims, although that is a risk and does occasionally occur, but a collaborative relationship between researchers and policymakers to craft solutions that adequately identify and address the issues. This is significant because of the role target-population recommendations serve in influenza management during seasonal epidemics and in the event of pandemics. As I discussed during the historical review of pandemics in chapter one, the influenza virus is unpredictable both in its mortality and attack rates. Having a process that quickly adapts to new evidence allows for the vaccine to be distributed to those who need it most; be it those at the highest risk or those required to preserve the functioning of society. This process must also be capable of communicating the rationale for the target-populations.

The WHO and CDC both use policymaking processes that require research to be reviewed prior to the implementation of recommendations. Although the processes used to determine the target-populations are evidence-based; I am suggesting that there is room for improvement in the process. The current processes have led to

recommendations that are criticized for being based on weak evidence.[578] While these criticisms could be due, in part, to a misunderstanding of the GRADE recommendation process, such criticism adds weight to the belief that the influenza vaccine is unncessary for those outside of the target-populations.[579] Additionally, the seasonal influenza vaccine is not well utilized even when supplies are widely available. My proposed changes address the criticisms of the current recommendations and have the potential to increase vaccination rates by increasing trust. Trust, as discussed in chapter five, is required for compliance with any public health policy but particularly the target-population recommendations. The target-population recommendations do not mandate vaccination and rely on compliance for success. My proposals are built upon the completion of aim one requiring the analysis of the research used to support target-population recommendations and the current research evaluation methodologies because in order for evidence-based policy to be successful it must be founded on high-quality research. My proposals involve changes to the evidence evaluation methodology and communication between researchers, policymakers, and the public. These improvements will address the current criticisms of the target-population recommendations by ensuring that research is fairly evaluated, regardless of the type of research. Improving the communication between researchers, policymakers, and the public has the potential to not only increase

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[578] Paul E. Alexander, et al., "World Health Organization Recommendations Are Often Strong Based on Low Confidence in Effect Estimates." *Journal of Clinical Epidemiology* 67, no. 6 (June 2014): 629-34.; Paul E. Alexander, et. al., "World Health Organization Strong Recommendations Based on Low-Quality Evidence (Study Quality) Are Frequent and Often Inconsistent with Grade Guidance." *Journal of Clinical Epidemiology*, accessed January 16, 2016, http://www.sciencedirect.com/science/article/pii/S089543561400417X.

[579] Information on the GRADE recommendation process is available in the appendix to chapter four.

research utilization within policymaking but also better addressing the concerns of the public regarding vaccine use.

Proposal 1: Adapt the GRADE methodology to create a greater balance between RCT and other research types for influenza vaccine research.

A comprehensive evidence evaluation needs to consider all types of research and provide a balanced rating. I have chosen to use GRADE as a foundation because it is well accepted within the research community and can be adapted for vaccine research. I recommend four main changes to GRADE. First, the use of appropriate PCORI-endorsed checklists. While checklists do not evaluate quality per se, they do help ensure that certain reporting and conduct criteria are met. Utilizing the checklists within the evidence evaluation methodology provides an initial review to ensure that basic accepted fundamentals have been met. Second, the de facto hierarchy would be removed to allow for a balanced evaluation of research from the onset. Research would be rated as Good, Fair, or Unacceptable based on the fulfillment of study specific criteria and the application of upgrading and downgrading criteria. Research would be evaluated based upon its quality of conduct and reporting without preference towards particular study types. An exceptional observation study would be viewed and assessed on its merits as would a RCT. Third, clear expectations of study quality, similar to the USPSTF, would be provided for each type of study. These criteria would spell out what is required for a study to be considered good, fair, or unacceptable; allowing for transparent evaluation. Finally, detailed criteria for up and downgrading research would be provided. This change addresses one of the limitations of GRADE that the up and downgrading criteria

can be vague.[580] These changes will allow for a comprehensive research program evaluation. Implementation of these changes would result in the following process:

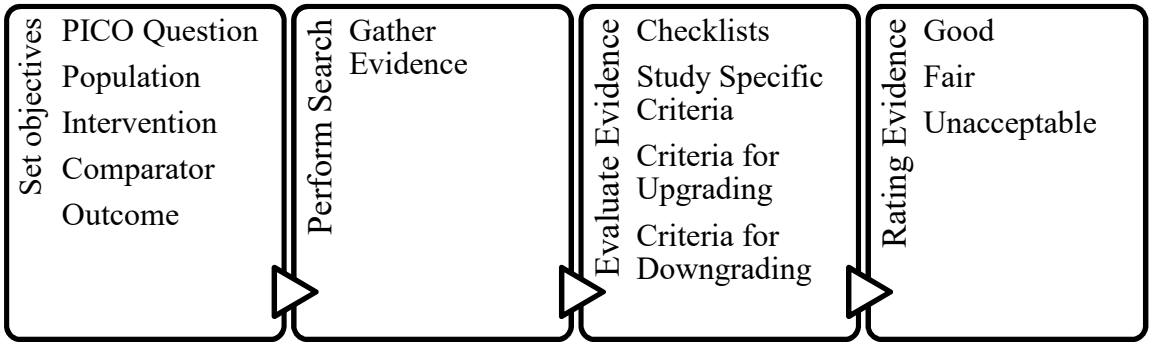

FIGURE 5: ADAPTED RESEARCH EVALUATION PROCESS

This process would allow for a balanced evaluation of any type of research. Appropriately evaluating the research used to determine the target-population recommendations will allow for a more accurate critique of the recommendations and identification of knowledge gaps. Improving the evaluation process can, in turn, lead to improvements in the recommendations and public communication.

Proposal 2: Use of the rhetorician's skill set to improve communication regarding influenza vaccine research.

Communication and trust are two intrinsically tied issues in evidence-based policymaking.[581] This holds particularly true for public health initiatives that require

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[580] Gordon H. Guyatt, et al., "GRADE Guidelines: 4. Rating the Quality of Evidence; study Limitations (Risk of Bias)." *Journal of Clinical Epidemiology* 64, no. 4 (April 11, 2011): 407–15. doi:10.1016/j.jclinepi.2010.07.017.

[581] Trisha Greenhalgh, and Jill Russell, "Evidence-Based Policymaking: A Critique." *Perspectives in Biology and Medicine* 52, no. 2 (2009): 304–18, 305. doi:10.1353/pbm.0.0085.; Christopher J. Jewell, and Lisa A Bero, "'Developing Good Taste in Evidence': Facilitators of and Hindrances to Evidence-Informed Health Policymaking in State Government." *The Milbank Quarterly* 86, no. 2 (June 2008): 177–208, 188-189. doi:10.1111/j.1468-0009.2008.00519.x; Louis W. Niessen, Els W.M Grijseels, and Frans F.H Rutten, "The Evidence-Based Approach in Health Policy and Health Care Delivery." *Social Science & Medicine* 51, no. 6 (2000): 859–69, 862. doi:10.1016/S0277-9536(00)00066-6.

voluntary compliance for success. Research results are not well communicated to policymakers, or the public contributes to the value of research being questioned, as discussed in chapter two. The research needs of policymakers are not well communicated to the scientific community leading to the available research being under-utilized and criticized as irrelevant. As discussed in chapter two, policymakers have a difficult time accessing clinical research because it is written for other scientists, not for policymakers and the lay public. The public distrusts both policymakers and researchers due to the lack of transparency in the policymaking process and the discovery of past research abuses. The Tuskegee Syphilis Study still causes distrust of research and the medicine in the African American community. Henry Beecher's landmark "Ethics in Clinical Research" article was printed fifty years ago, but the research community has faced public scandals since which have eroded the public's trust. I recommend the use of the rhetorician's skill set to improve communication regarding influenza vaccine research. Improvement of communication may lead to more meaningful utilization of research, the undertaking of more relevant research, and improved trust among all parties.

The rhetorician's skill set is built upon a broad intellectual foundation including the humanities, science, and policy. Communication, logic, and reasoning are the three main skills. Those who possess the rhetorician's skill set are able to analyze and discuss a broad range of topics. Engaging in discourse allows the full range of issues on the topic at hand to be discovered. Common ground can be reached by using communication and reasoning

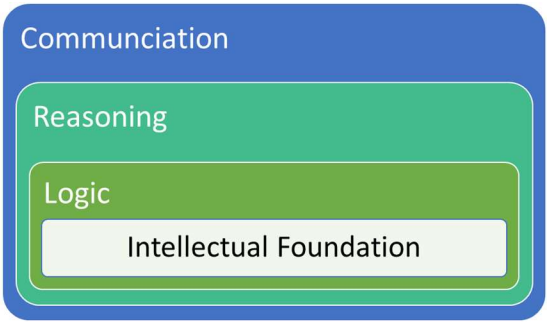

FIGURE 6: RHETORICAN'S SKILL SET

skills while embracing didactic and hermeneutical methods. This would allow for the creation of a policy that addresses the concerns of the public while utilizing high-quality, relevant research. Rhetoric is no longer the purview of the politician or even the responsibility of a particular group. The rhetorician's skill set can, and should, be used by all groups to further their goals. As I stated in chapter three, the anti-vaccine and vaccine skeptic communities have, perhaps unknowingly, well utilized the rhetorician's skill set to their benefit. Scientists and policymakers need to utilize the same skills to counter these dangerous arguments.

One specific area where the rhetorician's skill set can be applied is the communication of the WHO and CDC recommendations. CDC and WHO recommendations are not written in a manner easily accessible to the lay public. This is somewhat understandable as their main audience is clinicians and policymakers. However, as it is the lay public who is making the determination to vaccinate or not, the information must be better presented to them. Communication of the evidence base allows policymakers to show that their recommendations are unbiased and lends support to the argument that they are just. Clearly communicating the evidence also allows the public to draw their own conclusions regarding the decision to vaccinate, supporting personal autonomy. GRADE's Summary of Findings tables have been designed as a way to communicate evaluation findings and support recommendations. However, they require deep familiarity with the GRADE process and are not useful as standalone summaries for policymakers or the public. As I laid out in chapter two, I see communication being improved in two segments, pre- and post- pandemic. Pre-pandemic actions would focus on increasing overall vaccination rates, addressing the concerns of

parents, caregivers and the general public on vaccine safety, influenza virus misconceptions and the importance of vaccination. Post-pandemic actions would focus on target-population and social distancing. Social media would be systematically engaged throughout to deliver communication via user-friendly platforms. Scientific information would be shared not just in raw data but in how that data impacts people, how vaccines save lives and what the personal cost of refusing vaccination is.

The final aim of this project is the development an ethical justification to support the use of target-population recommendation for influenza vaccines. The ethical justification for the target-population recommendations is significant because the recommendations limit access to a potentially lifesaving intervention. Policymakers not only have an obligation to create ethical policy but the ethical justification impacts the likelihood that the public will trust and comply with the recommendations. The public must trust that the vaccine is not only safe and effective but that the distribution of the vaccine is fair.

I argue that the target-population recommendations for influenza vaccination are fair and equitable for three reasons. First, the target-population recommendations are based on the best evidence currently available and evolve with changes in the evidence. Second, the target-population recommendations can be supported via the ethical theory of utilitarianism. Finally, the target-population recommendations satisfy the principle of justice. These arguments apply even if the recommendations change in the event of a shortage caused by manufacturing delays and a pandemic.

The main purpose of the influenza vaccine is the prevention of severe illness and death. The target-population recommendations are guided by the ethical frameworks of

justice and utilitarianism to fulfill both of these goals. The full analysis is provided in chapter five and briefly summarized in the table below.

Table 7: Summary of Ethics Argument

	Justice Argument	Utility Argument
Prevention of severe illness and death by prioritizing the target-populations.	Target-populations for influenza vaccination benefit the least advantaged members of society and therefore implicates the Rawls' Difference Principle.	The target-population recommendations promote the Greatest Happiness Principle by increasing health in those most at risk, increasing overall health by preventing the spread of disease, while still allowing individual choice by not mandating vaccination.
	Target-population recommendations treat all persons who fall under them equally; if a person belongs to a group that is at increased risk for severe infection from the influenza virus, then they would receive priority allocation during a vaccine shortage	
Preservation of essential services by prioritizing healthcare workers and first responders.	The prioritization of healthcare workers and first responders would be justified through the original position. In this case, the common goal would be the preservation of essential services during a pandemic. The prioritization of healthcare workers and first responders would be accepted because it promotes health, opportunities, and liberties of all by reducing the risk of infection while preserving public services.	The Greatest Happiness Principle would support the preservation of essential services (healthcare workers, first responders, etc.) over those at risk for suffering in the event of a pandemic to ensure the ongoing functioning of society.

	Those required to perform essential duties such as healthcare workers and first responders receive priority over those at greater risk. This would not cause a conflict under formal justice as is a determination of equality that can be consistently and impartially applied.	

Where these ethical frameworks potentially falter is against an argument of liberty. Liberty is one of the most fiercely protected rights and both in the positive for having access and negative as to not being forced to take any action. Immunizations in the United States can only be federally mandated for members of the armed services. Personal autonomy will always determine immunization status for private citizens in the United States, although some employers require certain immunization. Personal autonomy is why a balanced and accurate evaluation of the evidence base for the target-population recommendations and a comprehensive communication plan is needed. People will chose to receive immunizations when they understand the threat of the underlying disease and that the vaccination is both safe and effective. My proposals are the first step in improving influenza vaccination policy to increase vaccination rates and reduce the public health and socioeconomic burdens of influenza infection.

FUTURE DIRECTIONS

This project laid the groundwork for improving evidence-based policymaking for influenza vaccine target-population recommendations by analyzing the recommendations,

determining the potential areas for improvement and proposing improvements. The next steps require further development and piloting of these proposals.

The proposed changes to the GRADE methodology require further development and piloting. The study-specific criteria and criteria to up and downgrade studies should be developed in collaboration with researchers and, ideally, the involvement of the GRADE working group. The USPSTF study specific criteria provided in the appendix provides a starting point for these discussions.

Implementation of the rhetorician's skill set into policymaking would require a combination of training and pilot projects. Training would have to occur for both policymakers and researchers. A training curriculum would have to be built for each group, facilitators located, and participants enrolled. This training should utilize a multidisciplinary team.

The project can be expanded to include other vaccines. The influenza vaccine is not the only vaccine that faces shortages; this project could be used to analyze target-populations for almost any vaccine. Applying the ethical analysis in a country that does not have the resources of the United States would also be an interesting outgrowth of this project.

CONCLUSION

In a given year, anywhere between 5 and 20 percent of the population of the United States will be infected with the influenza virus.[582] Influenza creates a yearly economic burden of approximately 87 billion dollars, with 10.4 billion being direct

[582] Flu.gov, "Seasonal Flu," accessed January 26, 2015, http://www.flu.gov/about_the_flu/seasonal/

medical costs.[583] In 2000, the Centers for Disease Control and Prevention (CDC) published a paper estimating approximately 114,000 hospitalizations due to influenza each year.[584] The number of deaths is more difficult to estimate due to inaccurate reporting and misdiagnosis, but the CDC estimates an average between three and forty-nine thousand deaths per year.[585] Literature suggests that a moderate to severe pandemic could cost over a million lives in the United States alone.[586] Vaccination saves lives and prevents suffering, but it would take almost two years to fully vaccinate the US population against a novel influenza strain with current manufacturing capabilities.[587] Target-population recommendations allow for the goals of vaccination (prevention of severe illness and death and the preservation of essential function) to be met during a vaccine shortage.

Target-population recommendations for the influenza vaccine can be improved with the more balanced research evaluation methodology and improved communication strategy proposed by this project. My proposed changes address the criticisms of the influenza vaccine as ineffective and the target-population recommendation as based on poor quality evidence by facilitating evidence-based policies. These criticisms are

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[583] Noelle-Angelique M. Molinari et al., "The Annual Impact of Seasonal Influenza in the US: Measuring Disease Burden and Costs," *Vaccine* 25, no. 27 (June 28, 2007): 5086–96, doi:10.1016/j.vaccine.2007.03.046

[584] Centers for Disease Control and Prevention, "Seasonal Influenza-Associated Hospitalizations in the United States" http://www.cdc.gov/flu/about/qa/hospital.htm.

[585] Centers for Disease Control and Prevention, "Estimating Seasonal Influenza-Associated Deaths in the United States: CDC Study Confirms Variability of Flu." http://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm.

[586] Kristin L. Nichol, and John J. Treanor, "Vaccines for Seasonal and Pandemic Influenza " *Journal of Infectious Disease* 194 Suppl 2(2006):S111-S118, S112.

[587] Assuming 2 million doses produced a week. James Halder, "Public Health Strategies for Distribution of Influenza Vaccine during an Influenza Pandemic" *Yale Journal of Biology and Medicine* 78 (October 2005): 273-82, 275.

addressed by allowing the research used to determine the target-population recommendations be evaluated in a balanced manner that is communicated to the public in a clear, understandable manner. Improving the evaluation of the research used as evidence to justify the recommendation and communication between researchers, policymakers, and the public can close knowledge gaps, increase trust in the influenza vaccine, and most importantly increase vaccination rates.

Appendix A: Appendix to Chapter One

The FDA has approved the following trivalent influenza vaccines:[588]

Trade Name	Manufacturer
Afluria	CSL Limited
Agriflu	Novartis
FLUAD	Novartis (adjuvanted)
Fluarix	Glaxo Smith Klein
Flublok	Protein Science
FluLaval	ID Biomedical Corp. of Quebec
Fluvirin	Novartis
Fluzone	Sanofi
Flumist	MedImmune (Intranasal)

The FDA has approved the following quadrivalent influenza vaccines[589]:

Trade Name	Manufacturer
FluMist Quadrivalent	MedImmune
Fluarix Quadrivalent	Glaxo Smith Klein
Fluzone Quadrivalent	Sanofi Pasteur
FluLaval Quadrivalent	ID Biomedical Corp. of Quebec

[588] Groshkoph, et al., "Prevention and Control of Influenza with Vaccines"
[589] Groshkoph, et al., "Prevention and Control of Influenza with Vaccines"

Appendix B: Appendix to Chapter Four

USPSTF CRITERIA

Systematic reviews are evaluated based upon the comprehensiveness of sources considered, the search strategy used, standard appraisal of included studies, and validity of conclusions, timing, and relevance of the studies.[590] To be considered a good quality review, the review should have a comprehensive search strategies, explicit and relevant selection criteria, standard appraisal and valid conclusions.[591] When a systematic review lack comprehensive sources and search strategies but is a recent, relevant review that is not clearly biased; its is rated fair by the USTFPS.[592] Poor systematic reviews have clear bias, are untimely, and/or irrelevant.

A well-designed case-control study includes accurate ascertainment of cases, nonbiased selection of cases/controls with exclusion criteria applied equally to both, response rate diagnostic testing procedures applied equally to each group, measurement of exposure accurate and applied to each group, appropriate attention to potential confounding variable.[593] A case-control study can be considered good when the study is well-designed, the response rate is equal to or greater than 80 percent, accurate diagnostic procedures and measurements applied equally, appropriate attention to confounding variables. When the case-control study is recent, relevant and without major selection or diagnostic workup bias but response rate less than 80 percent or has attended to some but not all important confounding variables the study would be rated as fair.[594] A poorly rated study occurs when major selection or diagnostic workup bias, response rate less than 50 percent or inattention to confounding variables.[595]

Well-designed RCTs and cohort studies require adequate assembly of comparable groups via randomization or consideration/control of confounders, maintenance of comparable groups, important differential loss to follow up or overall high loss to follow-up, measurements equal, reliable, and valid, clear definition if interventions, all important outcomes considered, analysis adjustments for potential confounders for cohort studies or intention to treat analysis of RCT.[596] Studies that can be rated as good meet all of the criteria for being well designed. Fair studies generally have comparable groups are assembled initially but some question on difference in follow-up, requirement instruments are acceptable and generally applied equally, some but not all important outcomes considered.[597] When fatal flaws are present, the study must be rated as poor.

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[590] Siu and LeFevre. "U.S. Preventive Service Task Force Procedure Manual" 69.
[591] Siu and LeFevre. "U.S. Preventive Service Task Force Procedure Manual" 69.
[592] Siu and LeFevre. "U.S. Preventive Service Task Force Procedure Manual" 69.
[593] Siu and LeFevre. "U.S. Preventive Service Task Force Procedure Manual" 69-70.
[594] Siu and LeFevre. "U.S. Preventive Service Task Force Procedure Manual" 70.
[595] Siu and LeFevre. "U.S. Preventive Service Task Force Procedure Manual" 70.
[596] Siu and LeFevre. "U.S. Preventive Service Task Force Procedure Manual" 70.
[597] Siu and LeFevre. "U.S. Preventive Service Task Force Procedure Manual" 70.

GRADE RECOMMENDATIONS

The GRADE process continues past evaluating the evidence to applying that evidence to make recommendations. The direction and strength of the recommendation is determined based upon the strength of the evidence in relation to the outcomes. Outcomes are selected from the outset and classified as critical and important but not critical.[598] Recommendations can be strong, conditional, discretionary, qualified or for research only.[599] Recommendations should be written to specific the population, comparator, be phrased in active voice, include the setting of the intervention and be presented in favor of a management approach.[600] An example of an influenza recommendation would be: pregnant women should receive the influenza vaccine in the second trimester. Within the justification, the recommendation should give the foundations and state foundations assumptions about the values and preferences that underlie recommendations for target-population.[601] If the panel is highly confident in the balance between desirable and undesirable consequence they make a strong recommendation for or against the intervention.[602] A strong recommendation is made when they believe that all or almost all informed people would make the recommended choice for or against the recommendation.[603] In policymaking, a strong recommendation implies that variability in clinical practice between individual or regions would be inappropriate, but does not correlate to priority for implementation.[604] Not all panels chose to make recommendations; if the evidence does not clearly support a particular intervention, the panel may choose to forgo making a recommendation.[605] If there is sufficient cause to believe that additional research will reduce uncertainty and be a good value for the investment, the panel may decide to recommend the intervention for research only, although this designation is rare.[606]

SYSEMATIC REVIEW PROTOCOL

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[598] Jeff Andrews, et al. "GRADE Guidelines: 14. Going from Evidence to Recommendations: The Significance and Presentation of Recommendations." *Journal of Clinical Epidemiology* 66, no. 7 (April 11, 2016): 719–25, 720. doi:10.1016/j.jclinepi.2012.03.013.

[599] Andrews, et al. "GRADE Guidelines: 14" 720.

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Systematic Review of Influenza Vaccine Efficacy Studies

Background

Description of the Condition

The influenza virus infection causes respiratory illness ranging in severity from subclinical to fatal. Patients over the age of sixty-five, under the age of two, and patients with co-morbid medical conditions, such as chronic cardiac and pulmonary illnesses, experience the highest rate of severe illness. (Fiore, Uyeki et al. 2010)). The influenza virus infects an estimated 5 to 10 percent of adults and 20 to 30 percent of children worldwide. (World Health Organization, 2005). Countries in temperate climate tend to experience cyclical epidemics in the winter whereas countries in tropical climates may have unpredictable, year-round outbreaks (World Health Organization, 2005).

Influenza A and B viruses are transmitted mainly via aerosolized droplets and occasionally through contact with virus contaminated fomites (World Health Organization, 2012). Influenza A viruses have higher capacity for human-to-human transmission and historically create major pandemics every ten to forty years due to antigenic shift. (World Health Organization, 2012) Influenza's incubation period lasts between one and four days. Adults generally shed virus for a few days; however children and infants shed the virus for up to two weeks, increasing opportunities for virus transmission. Symptoms of infection can include fever, cough, sore throat, runny nose, headache, muscle and joint pain, severe malaise; although not all infected persons exhibit the full range of symptoms and asymptomatic carriers can still spread infection. Secondary bacterial pneumonia is a frequent complication (World Health Organization, 2012). Morbidity and mortality of influenza is likely underestimated in the tropics and subtropics due limited surveillance and reporting (World Health Organization, 2012).

Description of the Intervention

Vaccination is an effective method for preventing influenza virus infections, as well as the resulting complications, and is recommended for all persons over six months of age without contraindications. Effectiveness (used here as the success in preventing influenza-like-illness) and efficacy (used here as success in preventing laboratory confirmed influenza infection) of the seasonal influenza vaccine are dependent upon several factors including the immunocompentece of the vaccine recipient and the degree of similarity between the viruses in circulation and in the vaccine. (Fiore, Uyeki et al. 2010). In seasons with good match between the virus strains included in vaccines and circulating viruses, influenza vaccine effectiveness is 70-80% against influenza virus infection (Fiore, Uyeki et al. 2010). The World Health Organization provides recommendations on the strains to be included in the seasonal influenza vaccine in February for the northern hemisphere and August for the southern hemisphere.

The most commonly used influenza vaccine formulations are trivalent inactivated (TIV) and live attenuated (LAIV). TIV is licensed for use in all patients who do not have a contraindication for vaccination. LAIV may be used only in healthy, non-pregnant persons between the ages of two and forty-nine as the safety and efficacy in high risk populations has not been adequately established for licensure. Infants under six months of age cannot be vaccinated against influenza. Children under the age of nine who have not

been previously vaccinated against influenza should receive two injections, at least one month apart, which creates a logistical challenge for influenza vaccination programs.

Adverse events of the influenza vaccine are typically mild and include tenderness at the injection site and fever. Severe adverse events are typically rare and include transient systemic reactions, a slightly higher risk of Guillain-Barre Syndrome, infection, and febrile seizures.

How the Intervention might work

Influenza vaccines work by eliciting a strain specific antihaemagglutinin immune response and are recommended annually due to antigenic drift, but protection against included strains can last for up to 6-8 months post vaccination. (WHO 2005).

Why it is important to do this review

Knowledge of relevant seasonal influenza vaccine research is vital for influenza vaccine policy making. This project would collect all relevant influenza vaccine clinical trial data from phase III and phase IV trials, abstract key data, and to consolidate articles in a form that would make the evidence available for policy makers at WHO and in Member States.

Objectives

To identify the clinical endpoints of influenza vaccine efficacy studies indexed in PubMed, written in English, and published from 1980 through 2014 to assess the degree of standardization and the severity of illness represented.

Methods

Criteria for considering studies for this review

To be considered for inclusion in this review studies prospective, individual randomized controlled trials, must be written in English, address vaccine efficacy via laboratory confirmed influenza infection and have been published between 1980 and 2015.

Inclusion criteria

- Randomized controlled clinical trials of influenza vaccine with laboratory confirmed influenza virus infection.

Exclusion criteria

- Non-English
- Prior to 1980
- No lab confirmation
- Not randomized

Types of Studies

- Randomized controlled trials

Types of Participants

- All vaccine eligible populations will be reviewed.

Types of Outcome Measures

- Vaccine efficacy against influenza disease as shown through occurrence of laboratory- confirmed influenza virus infection in the vaccination group as compared to the control.

Search methods for identification of studies

We will conduct an electronic literature search applying the Patient, Population, Intervention, Comparator, Outcome, Timing and Settings (PICOTS) framework as outlined in Table 1. Electronic search strategies were developed and tested through an iterative process by an experienced medical information specialist in consultation with the review team. The database searched were PubMed and the CENTRAL database of the Cochrane Library on Wiley. Strategies utilized a combination of controlled vocabulary (e.g., "Influenza, Human," "Influenza A Virus ", "Influenza Vaccines") and keywords, including the specific names of the vaccines (e.g., H1N1, vaccine, FluMist). Vocabulary and syntax were adjusted across databases. We used a validated filter for randomized clinical trials and restricted results to the English language and the publication years 1980 to the present. Case reports, case series, case-control, cohort, and challenge studies were excluded. Our search criteria are listed in full in Appendix 1.

Data collection and analysis

Data will be abstracted a standardized form which will be designed and piloted by the study authors. Data abstraction will be verified by contacting the corresponding authors via email. One reviewer will screen titles and abstracts of all citations to identify all potentially eligible studies in the first screen. Full-text review was completed by the same reviewer as the second screen. Any question of study inclusion was determined by the second reviewer. The screening results and reasons for exclusion will be kept and are available for review. The study will be limited by the fact that only one reviewer was available.

We anticipate analysing the data using multiple categorizations. Participant types will be categorized by healthy volunteers, those with chronic conditions, and specific populations such as healthcare workers and institutional residents with ages being noted. Income status will be determined using the World Bank classifications for each country. WHO Region will be noted for each country. Funding source of the study will be categorized by government, industry, foundation or joint (multiple sources).

Collection Criteria will be categorized for analysis by the following:

- Present with Illness
- Any Respiratory illness
- Physician Discretion
- Multiple Respiratory and systemic symptoms
- Typical criteria such as SARI or ILI.
- None reported

Endpoints will be categorized for analysis by the following:

- Severe Outcomes (as defined by hospitalization, pneumonia, or death)
- Symptomatic Laboratory Confirmed Influenza
- Laboratory Confirmed Influenza
- Serological Response

We anticipate that the proposed analyses will allow for assessment of the degree of standardization and the severity of illness represented in influenza vaccine clinical trials.

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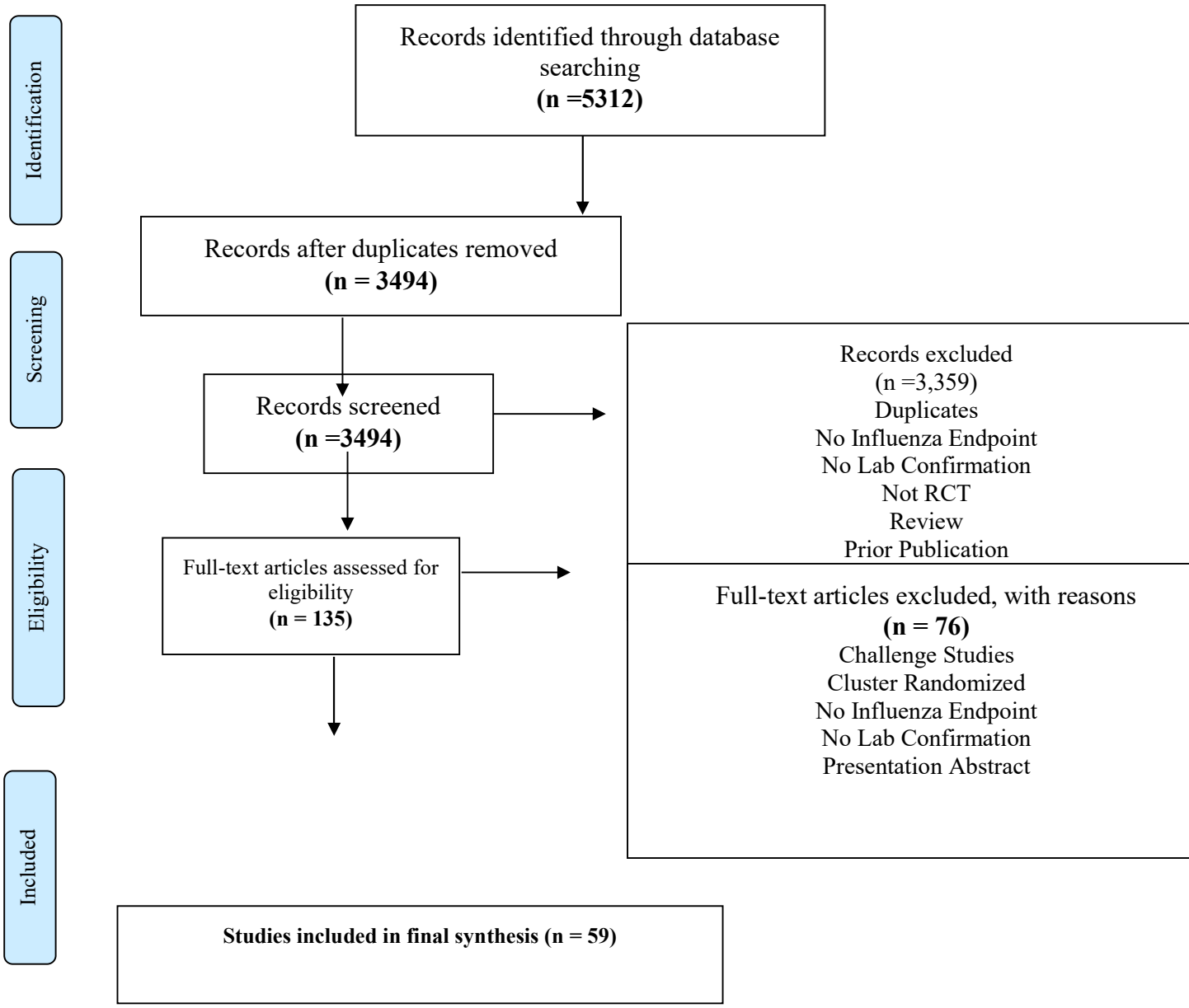
PICOTS Framework

	Components	**Characteristics**
P	**Population**	All Populations
I	**Intervention**	Influenza Vaccine
C	**Control**	Placebo or Vaccine Control
O	**Outcomes**	Efficacy against culture confirmed influenza
T	**Timing**	Trials will be restricted to those ≥ 1980.
S	**Setting**	Inpatient, Outpatient

PRISMA Flow Chart



Search Criteria Influenza Vaccines

Final Strategies
2015 Jul 6

PubMed

Search	Query	Items found
#27	Search #25 AND #26	2869
#26	Search ("1980"[Date - Publication] : "3000"[Date - Publication])	19443603
#25	Search #23 AND #24	3097
#24	Search "english"[Language]	20559726
#23	Search #20 NOT (#21 OR #22)	3321
#22	Search letter [pt] NOT (letter [pt] AND randomized controlled trial [pt])	876245
#21	Search comment [pt] OR editorial [pt] OR interview [pt]	911355
#20	Search #18 NOT #19	3393
#19	Search Animals [mesh] NOT (Animals [mesh] AND Humans [mesh])	4017863
#18	Search #11 AND #17	3518
#17	Search #12 OR #13 OR #14 OR #15 OR #16	1073655
#16	Search trial [ti]	139855
#15	Search single blind* [tw] OR double blind* [tw] OR triple blind* [tw] OR single mask* [tw] OR double mask* [tw] OR triple mask* [tw] OR single dumm* [tw] OR double dumm* [tw] OR triple dumm* [tw]	187644
#14	Search randomised [tw] OR randomized [tw] OR randomly [tw] OR RCT [tw] OR RCTs [tw] OR placebo* [tw]	828440
#13	Search "clinical trials as topic" [mesh]	286820
#12	Search "controlled clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type]	474769
#11	Search #6 AND #10	33703
#10	Search #7 OR #8 OR #9	376615
#9	Search Imuvac [tw] OR Influvac [tw] OR AdimFlu* [tw] OR Celvapan [tw] OR Vepacel [tw] OR Inflexal* [tw] OR HNVAC [tw] OR "M-001" [tw] OR Cantgrip* [tw] OR Afluria [tw] OR Fluvax [tw] OR Panvax [tw] OR Ultrix [tw] OR "GC FLU" [tw] OR "Green Flu-S" [tw] OR Adjupanrix [tw] OR Arepanrix [tw] OR Fluarix [tw] OR FluLaval [tw] OR Pandemrix [tw] OR Prepandrix [tw] OR Pumarix [tw] OR CEPAS [tw] OR Viroflu [tw] OR FLUENZ [tw] OR FluMist [tw] OR Grippol [tw] OR Aflunov [tw] OR Agriflu [tw] OR Agrippal [tw] OR Celtura [tw] OR Flucelvax [tw] OR Fluvirin [tw] OR Focetria [tw] OR Foclivia [tw] OR Optaflu [tw] OR AdeVac* [tw] OR Fluval [tw] OR Enzira [tw] OR Flublok [tw] OR Fluzone [tw] OR IDflu [tw] OR Intanza [tw] OR Panenza [tw] OR Vaxigrip [tw] OR NASOVAC* [tw] OR AnFlu* [tw] OR Panflu* [tw] OR Vaccinum Influenzae [tw] OR Vaxiflu* [tw] OR "Split	716

	Virion" [tw]	
#8	Search vaccin* [tw] or innoculat* or immuniz* [tw] OR immunis* [tw]	376601
#7	Search Influenza Vaccines [mesh]	17121
#6	Search #1 OR #2 OR #3 OR #4 OR #5	107750
#5	Search H1N1 [tw] OR PH1N1 [tw] OR H3N2 [tw] OR AH1N1 [tw] OR AH3N2 [tw]	18475
#4	Search Influenza B Virus [mesh]	3141
#3	Search Influenza A Virus [mesh]	33661
#2	Search influenza* [tw] OR flu [tw] OR grippe [tw]	107588
#1	Search Influenza, Human [mesh]	37363

Cochrane Library

Search Name: Influenza Vaccines
Date Run: 06/07/15 16:59:30.940
Description: WHO - 2015 Jul 6

ID Search Hits
#1 [mh "Influenza, Human"] 1388
#2 (influenza* or flu or grippe):ti,ab,kw 6083
#3 [mh "Influenza A Virus"] 737
#4 [mh "Influenza B Virus"] 227
#5 (H1N1 or PH1N1 or H3N2 or AH1N1 or AH3N2):ti,ab,kw 847
#6 {or #1-#5} 6086
#7 [mh "Influenza Vaccines"] 1313
#8 (vaccin* or innoculat* or immuniz* or immunis*):ti,ab,kw 14251
#9 (Imuvac or Influvac or AdimFlu* or Celvapan or Vepacel or Inflexal* or HNVAC or "M-001" or Cantgrip* or Afluria or Fluvax or Panvax or Ultrix or "GC FLU" or "Green Flu-S" or Adjupanrix or Arepanrix or Fluarix or FluLaval or Pandemrix or Prepandrix or Pumarix or CEPAS or Viroflu or FLUENZ or FluMist or Grippol or Aflunov or Agriflu or Agrippal or Celtura or Flucelvax or Fluvirin or Focetria or Foclivia or Optaflu or AdeVac* or Fluval or Enzira or Flublok or Fluzone or IDflu or Intanza or Panenza or Vaxigrip or NASOVAC* or AnFlu* or Panflu* or Vaccinum Influenzae or Vaxiflu* or "Split Virion"):ti,ab,kw 192
#10 {or #7-#9} 14254
#11 #6 and #10 Publication Year from 1980 to 2015 2760

DSR - 35
DARE - 73
CENTRAL – 2443 [RCTs/CCTs]
Methods – 21
HTA – 35
NHS EED - 153

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