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Tiara J. Harms Date

GRADING OF RECOMMENDATIONS, ASSESSMENT, DEVELOPMENT, AND EVALUATION (GRADE) FOR ACAM2000: A LICENSED SMALLPOX VACCINE FOR PERSONS AT RISK FOR ORTHOPOXVIRUS DISEASE

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An abstract of
A Thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements of the degree of
Master of Public Health in the Executive MPH program
2014

Abstract

GRADING OF RECOMMENDATIONS, ASSESSMENT, DEVELOPMENT, AND EVALUATION (GRADE) FOR ACAM2000: A LICENSED SMALLPOX VACCINE FOR PERSONS AT RISK FOR ORTHOPOXVIRUS DISEASE

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Despite smallpox eradication, orthopoxviruses still remain at the forefront of public health concern, as the potential for acquiring orthopoxvirus disease still exists; whether naturally, through inadvertent laboratory exposure, or intentional release. Protection is best achieved through vaccination with a vaccinia virus vaccine. In the United States (U.S.), the Advisory Committee on Immunization Practices (ACIP) is tasked with developing and providing expert written guidance on the use of vaccines and vaccine-related agents, approved by the Food and Drug Administration (FDA), for control of vaccine-preventable diseases in the U.S. civilian population. In 2008, ACAM2000 replaced Dryvax as the only FDA licensed and approved smallpox vaccine available for use in the U.S. for protection against orthopoxvirus disease. Despite ACAM2000 having been widely used since 2008, ACIP smallpox vaccination recommendations have not been updated since 2003. As the current recommendations are out of date, the need for development of new ACIP smallpox vaccination recommendations is paramount.

The purpose of this study was to utilize the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to determine the evidence type (quality) for ACAM2000 within the context of the policy question considered by the ACIP Smallpox Vaccine Workgroup: "Should ACAM2000 be recommended routinely for persons at risk for Orthopoxvirus disease?" Critical outcomes were determined through a modified Delphi analysis, and a systematic review of literature was conducted. Data from five randomized controlled trials were pooled using meta-analysis. Pooled risk ratios for cutaneous response and mild adverse events (MAE) outcomes indicated there was no difference in these outcomes occurring in individuals vaccinated with ACAM2000 or Dryvax. Serious adverse events (SAE) and myo/pericarditis resolved with sequelae were each less likely to occur in those vaccinated with ACAM2000, while myo/pericarditis resolved without sequelae was more likely to occur among individuals vaccinated with ACAM2000. Using GRADE, the overall evidence quality across all critical outcomes was determined to be of moderate quality. The results of this study will be made available to ACIP for final consideration, and will aid in forming U.S. policy regarding smallpox vaccinations for persons at risk for orthopoxvirus disease.

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ACKNOWLEDGEMENTS

First and foremost, I would like to thank my thesis committee, Dr. Jean O'Connor and Dr. Brett Petersen for their help, guidance, and editorial insight throughout this process. Specifically, I would like to thank Brett for enduring the past 2 (plus) years with me on this project. This is just as much a testament of your hard work and dedication (and frustration!) as it is mine. I simply can't thank you enough. I owe you ~~one~~ a lot.

I would also like to extend my heartfelt thanks to the EMPH faculty for allowing me to take a chance on myself during a time in my life when I had nothing to lose, and everything to gain, on a professional level. The professionalism of the faculty, as well as, their willingness to share their own knowledge, awareness, and experiences, will always be valued beyond measure.

Lastly, I would like to thank my family for their support during the course of this program. To my parents, Dwight and Colleen Morehead, you have always led by example, believed in me, and instilled in me the value of (quality!) education. If, in my lifetime, I make you half as proud to be my parents as I am to be your daughter, then I will consider my life a resounding success. And finally, to my husband, Brent Harms…you are my everything. There is no way on earth I could have done this without you. I know it wasn't always easy putting up with me during this program, but your unwavering support has carried me through to the very end. This crazy life adventure we share is truly amazing, and though we've been at it a while, it's still just beginning. I love you more than mere words on paper could ever express.

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CHAPTER 1
INTRODUCTION

Introduction & Rationale

The Advisory Committee on Immunization Practices (ACIP), established in 1964 by the Surgeon General of the United States (U.S.) Public Health Service, is tasked with developing and providing expert written guidance to the Director of the Centers for Disease Control and Prevention (CDC), as well as the Secretary of the U.S. Department of Health and Human Services (DHHS) on the use of Food and Drug Administration (FDA) approved vaccines, and vaccine-related agents, for control of vaccine-preventable diseases in the U.S. civilian population (Ahmed *et al*., 2011; Smith, 2010). The scope of guidance encompasses appropriate age for vaccine administration, dose and frequency of administration, the precautions and contraindications of vaccine use, as well as information on adverse events (Smith *et al*., 2010). Despite ACIP recommendations not carrying any legal mandate, they are widely regarded as national policy, and most of the responsibility for their implementation lies with state-level governments (Smith *et al*., 2010).

In 2010, ACIP voted to recommend to CDC / DHHS the adoption of a new framework for developing evidence-based recommendations based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Ahmed *et al*., 2011). At the time GRADE was adopted by ACIP, it had already been incorporated into the evidence-based systems used by many leading organizations including, the World Health Organization, Cochrane Collaboration, American Academy of Family Physicians, and American College of Physicians (Ahmed *et al*., 2011). The GRADE approach is based on a systematic and sequential assessment of the quality of evidence, followed by judgment regarding the balance between desirable and

undesirable effects, before deciding the strength of a recommendation (Ahmed *et al*., 2011). Through adoption of the GRADE framework, ACIP aimed to enhance the decision-making process by creating a more transparent, consistent, and systematic approach to development of vaccine recommendations (Ahmed *et al*., 2011). Application of the GRADE framework for the development of recommendations for the routine administration of ACAM2000 for persons at risk for orthopoxvirus disease is the focus of this study.

Problem Statement

Due to the potential for exposure to orthopoxviruses whether naturally, through inadvertent laboratory exposure, or intentional release, there is a significant public health need for protection of individuals against orthopoxvirus-associated diseases. As there is not a registry of laboratories that conduct orthopoxvirus research, the total number of people working with orthopoxviruses within a laboratory setting remains unknown. Additionally, there is no formal surveillance system in place to monitor the number of laboratory exposures, nor are exposures to an orthopoxvirus in a laboratory setting required to be reported to the CDC, unless that exposure was to a select agent, or the exposure results in an active orthopoxvirus infection (Reynolds, 2013). These factors create an element of uncertainty as to the actual number of people who may be at risk for orthopoxvirus disease, and who may potentially pose a risk to the greater population if infected.

Between 2004 and 2012, there were twenty-one cases of laboratory-related orthopoxvirus exposures reported to the CDC resulting in eleven confirmed infections (Reynolds, 2013). Of those twenty-one individuals exposed, only five had been vaccinated according to ACIP recommendations, and were subsequently protected from active infections (Reynolds, 2013). Between 2004 and 2009, one hundred thirty-four unique institutions had requested vaccinia virus

vaccine from the CDC for vaccination purposes, indicating the number of individuals that may be exposed to orthopoxviruses as a result of their occupation is high (Reynolds, 2013). Additionally, unvaccinated laboratorians who are exposed and become infected, could potentially be an exposure threat to individuals they come in contact with. In July 2008, an unvaccinated laboratorian experienced an accidental exposure, and proceeded to fall ill with fever and lesions. During the time the individual was ill and infectious, fifty-five people had potentially been exposed to lesion exudates, seven of which were individuals with underlying risk factors for severe outcomes from vaccinia infection (Reynolds, 2013). These cases highlight the importance of vaccination against orthopoxviruses, as well as the need for adherence to ACIP vaccination recommendations for persons at risk for orthopoxvirus disease. Specifically, recommendations that identify ACAM2000, the only U.S. FDA licensed and approved smallpox vaccine available, as the vaccine to be utilized in the protection against orthopoxvirus disease.

Study Framework

This study is rooted in the GRADE framework, which offers a transparent and structured process for developing and presenting summaries of evidence, as well as quality of evidence, for recommendations in healthcare (Guyatt *et al*., 2011). GRADE provides those tasked with developing guidelines and recommendations with a comprehensive framework for carrying out the steps involved in development of recommendations (Guyatt *et al*., 2011). The framework specifies the approach that should be taken to framing policy questions, choosing health outcomes of interest (both benefits and harms) and rating their importance, and evaluating the evidence for those health outcomes. Finally, the evaluated evidence, are combined with considerations of the values and beliefs held by patients and society to finally arrive at recommendations (Guyatt *et al*., 2011).

Purpose Statement

The purpose of this study was to apply the GRADE approach in the development of the ACIP recommendations for administration of ACAM2000 to persons at risk for orthopoxvirus disease. The study aimed to assess, summarize, and rate the quality of evidence necessary for the ACIP Smallpox Vaccine Workgroup to make an informed decision regarding the development of smallpox vaccination recommendations. The specific objectives of this study were:

I. To develop an appropriate policy question for the population (P), intervention (I), control (C), and outcome (O) (PICO) of interest and conduct a systematic review of literature that satisfies the PICO.
II. To identify the outcomes of interest and rate the quality of evidence for each outcome across all studies satisfying the PICO, and assign a rating for the overall quality of evidence across all critical outcomes.
III. To identify the strengths, limitations and applicability of utilizing the GRADE approach for future smallpox vaccine vaccination recommendations.

Significance Statement

Through utilizing the GRADE approach, ACIP aims to bring transparency and an evidence-based structure to the process of developing vaccine recommendations. The ACIP recommendations developed based on the evidence graded within this study will likely be viewed, and implemented, as government policy for all persons at risk for orthopoxvirus disease. While numerous organizations have utilized the GRADE framework to develop policy and recommendations, it has yet to be determined whether this "one size fits all" approach is applicable, and useful, to all vaccine recommendations considered by ACIP. The analysis put

forth in this study will highlight areas future ACIP workgroups may need to consider, especially those tasked with making recommendations for vaccines against viral diseases, such as smallpox, for which there may be considerable study limitations and constraints.

Definition of Terms and Abbreviations

Benefits: Desirable effects (e.g. protection, savings) experienced as a result of the intervention of interest.

Evidence Profile (EP): A detailed quality assessment that includes the detailed judgment of each factor that determines the quality of evidence for each outcome and provides a record of judgments that were made by the reviewer(s) or guideline authors (Guyatt *et al*., 2011).

Harms: Undesirable effects (e.g. costs, adverse effects) experienced as a result of the intervention of interest.

Imprecision: Quality of evidence rating category that refers to the extent to which the confidence in the effect estimate is adequate to support a particular decision. May result from studies having relatively few participants and few events that result in wide confidence intervals around the effect size (Ahmed, 2013).

Inconsistency: A measure of evidence quality where there is an unexplained heterogeneity in the magnitude of the effect size across studies (Ahmed, 2013).

Indirectness: A measure of evidence quality. Evidence may be considered indirect if the population within the study differs from the population of interest or if the intervention evaluated differs from the intervention of interest (Ahmed, 2013).

Mild Adverse Events (MAE): Outcomes of vaccination considered harmful. The MAE in this study includes those adverse events not specifically identified as SAE, inadvertent inoculation, or incidences of myo/pericarditis resolved with or without sequelae.

PICO: The Population (P), Intervention (I), Comparison (C), and Outcomes (O), (PICO) taken into consideration when evaluating evidence and formulating recommendations for a specific policy question.

Pooled Risk Ratio: Ratio of the risk of an event within interventions. (Deeks, Higgins & Altman, 2008).

Publication Bias: A measure of evidence quality regarding the systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies (Ahmed, 2013).

Risk of Bias: A measure of evidence quality and study limitation that may bias the estimates of the effect of an intervention on a health outcome. For randomized controlled trials this may include: allocation sequence generation (selection bias); allocation sequence concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); and selective outcome reporting (reporting bias) (Ahmed, 2013).

Serious Adverse Events (SAE): Outcomes of vaccination considered harmful. The SAE in this study include: postvaccinial encephalitis, eczema vaccinatum, progressive vaccinia, and generalized vaccinia.

Summary of Findings (SoF): A detailed assessment of the quality of evidence for each outcome. Provides a concise summary of the key information needed by those making a decision, and provides a summary of the key information underlying a recommendation (Guyatt *et al*., 2011).

CHAPTER 2
REVIEW OF LITERATURE

Introduction

This chapter reviews the relevant literature needed for the understanding, and effective execution, of grading the evidence required for the development of ACIP smallpox vaccination recommendations. Information regarding smallpox vaccine including development, costs, risks and concerns; development of U.S. immunization policy; and an overview of the GRADE approach will be discussed. This review concludes with a summary of the current public health problem, and the relevance of this study in addressing the issue.

Literature Review

Orthopoxviruses

Orthopoxviruses, members of the *Poxviridae* family and *Orthopoxvirus* genus of viral pathogens, are a group of large, double-stranded DNA viruses, which infect vertebrate hosts, and confer immunity due to their cross antigenicity (Buller & Palumbo, 1991; Costa *et al*., 2013). Having had significant impact on global public health in the past, orthopoxviruses, most notably those infecting humans such as variola (VARV), monkeypox (MPXV), cowpox (CPV), and vaccinia (VACV), still remain at the forefront of public health concern (Fenner *et al*., 1988). Variola, the etiological agent of smallpox, was one of the most important causes of morbidity and mortality worldwide, having been the cause of death for up to 500 million persons in the 20th century alone (Fenner *et al*., 1988; Weinstein, 2011).

At the height of transmission, and prior to effective vaccination and containment strategies, smallpox was endemic throughout the world with the exception of Australia and a few remote islands (Buller & Palumbo, 1991). Documented efforts to prevent the spread of smallpox via inoculation and variolation date back to the 6th century B.C. (Fenner *et al*., 1988). However,

it wasn't until 1796, when Edward Jenner showed via challenge inoculation that individuals who had previously been infected with CPXV were resistant to VARV, that vaccination became the primary defense against smallpox infection (Fenner *et al*., 1988).

Despite implementation of vaccination practices, smallpox remained as an endemic disease in nearly every country of the world through the early and mid 19th century (Fenner *et al*., 1988). The latter part of the 19th and early 20th centuries brought a decline in the number of smallpox cases seen worldwide due to increased vaccination, revaccination, as well as improved health services and other public health measures such as isolation and quarantine (Fenner *et al*., 1988). In 1959 the World Health Organization (WHO) established an intense global eradication campaign to eradicate smallpox (Fenner *et al*., 1988). Through this intensified international program of surveillance and vaccination, using VACV vaccines, smallpox was declared eradicated in 1980, and became the first infectious disease of humans to have been eradicated through deliberate global intervention (Greenberg & Kennedy, 2008; Fenner *et al*., 1988).

In the decades since, vaccinia viruses have subsequently become the prototype member of the orthopoxvirus genus and are now widely used not only as vaccines against other orthopoxviruses, but also as recombinant viruses used to express foreign proteins in eukaryotic cells and general research tools (Isaacs, 2012; Moss, 1996; Carroll & Moss, 1997). While routine prophylactic vaccination against smallpox ceased in the U.S. in 1971, and worldwide in 1980, ongoing public health issues surrounding emerging and re-emerging zoonotic orthopoxvirus associated diseases remains (Keckler *et al*., 2013). Recently, the Democratic Republic of Congo (DRC) has seen a rise in MPXV infections, while outbreaks of MPXV in both Sudan and the U.S. highlight the potential of MPXV to spread beyond the Congo basin (Keckler *et al*., 2013; Reynolds & Damon, 2012). Additionally, outbreaks of VACV in Brazil, CPXV in Europe, and

buffalopox in India are routinely observed and reported (Keckler *et al*., 2013). Finally, continued orthopoxvirus research and the potential threat of an intentional release of VARV, have made developing countermeasures against orthopoxvirus-associated disease a priority (Keckler *et al*., 2013). These countermeasures include not only further research efforts, but also development and implementation of public health policies such as vaccination recommendations for individuals at risk for orthopoxvirus disease as well (Keckler *et al*., 2013).

Smallpox Vaccine

Historically, U.S. smallpox vaccination policies were developed around the use of Dryvax, the first VACV vaccine approved for use in the U.S. in 1931 (Greenberg & Kennedy, 2008). Widely utilized during the smallpox eradication campaign in the Western Hemisphere and Africa, Dryvax was a first generation smallpox vaccine manufactured by Wyeth Laboratories (Marietta, PA) from lymph collected from the skin of calves that had been scarified with the New York City Board of Health (NYCBH) VACV strain (Monath *et al*., 2004; Handley *et al*., 2009). In 1978, production of Dryvax ended, leaving 15 million vaccine doses remaining in the U.S. after the suspension of routine smallpox vaccinations (Nalca & Zumbrun, 2010). In 1998, the U.S. initiated the development of a strategic national stockpile (SNS) of vaccines (Greenberg & Kennedy, 2008). During this time, the age of the remaining Dryvax stock, combined with the knowledge that production methods utilized to manufacture Dryvax had since been deemed unethical, due to the treatment of the animals utilized in the manufacturing process, and not in compliance with present-day good manufacturing standards and practices, led to the awareness that development of a new generation of smallpox vaccines was urgently needed (Greenberg & Kennedy, 2008; Handley *et al*., 2009). As a result, in 1999, the CDC awarded Acambis, Inc. (Acambis, Inc., of Cambridge UK, and Cambridge, MA, USA) a contract to secure 209 million

doses of a second-generation, cell-culture derived vaccine. Following the development and licensure of the new vaccine, ACAM2000, Wyeth Laboratories withdrew the vaccine license for Dryvax on February 29, 2008, and all remaining stocks of this vaccine were subsequently destroyed (CDC, 2008; Handley *et al*., 2009).

Development of ACAM2000 began with ACAM1000, a homogenous clonal isolate of vaccinia virus from the NYCBH parent strain (Handley *et al*., 2009). ACAM1000 was shown to be equivalently immunogenic to Dryvax, however, the MRC-5 (diploid human embryonic lung fibroblasts) cell line used for manufacturing was deemed not suitable for large-scale vaccine production (Handley *et al*., 2009). Therefore, seed stock of ACAM1000 (passage 7) was further grown and amplified in serum-free, large-scale manufacturing conditions in Vero (green monkey kidney) cells (Handley *et al*., 2009). Recognizing the potential for genetic change due to passage in a new cell line, the resulting virus was termed ACAM2000 and was shown to be genetically identical to ACAM1000 with equivalent immunogenicity and virulence profiles (Handley *et al*., 2009). In August 2007, ACAM2000 was licensed by the Food and Drug Administration (FDA), and became the replacement vaccine for smallpox vaccination within the U.S. (CDC, 2008).

Vaccination Concerns, Risks and Costs

In the U.S., the CDC is the only source of smallpox vaccine for civilians, as it is not commercially available (MMWR, 2001). Upon request, CDC will provide vaccine to the requesting institution, at the cost of the U.S. Government, for protection of laboratory and other health-care personnel who may be at risk for exposure to orthopoxviruses due to their occupation (CDC, 2001). Though the vaccine is provided free-of charge, administration of live VACV vaccines, such as ACAM2000, does come with serious safety concerns, as well as the potential of both physical and emotional costs. The risk for serious adverse events (SAEs) such as

generalized vaccinia, eczema vaccinatum, postvaccinial encephalitis, fetal vaccinia, and even death in vaccinated persons and their close contacts, though rare, are real (Rosenthal, Merchlinsky & Chowdhury, 2007). These post-vaccination risks have shown to impact compliance rates for vaccination recommendations of U.S. healthcare workers and laboratorians (Keckler *et al*., 2013). However, the potential protective benefits of vaccination with ACAM2000 during a smallpox outbreak, prophylactic vaccination of persons who are considered at high risk for exposure, as well as those individuals who may have recently been exposed to othopoxviruses, outweigh potential risks (Rosenthal, Merchlinsky, & Chowdhury, 2007).

In addition to SAE, many people have conditions that put them at increased risk for SAE such that a substantial proportion of the population may be unable to receive vaccination against orthopoxviruses (Walsh & Dolin, 2011). Currently, it is estimated that upwards of 25% of the U.S. population have conditions that might preclude vaccination with VACV including: immunosuppression, pregnancy, breast-feeding, HIV, atopic dermatitis or eczema, contact with household members who cannot receive VACV, as well as being under the age of 18 (CDC, 2001; CDC, 2003a). Risk of SAE's can be minimized through educating both providers and vaccinated individuals on proper care of the vaccination site, dressing changes, hand washing, as well as other measures to prevent vaccination transmission and autoinoculation (Rosenthal *et al*., 2007). When incorporated into a smallpox vaccination program, these activities have been shown to have significant impact on reducing the occurrence of SAE's (Rosenthal *et al*., 2007).

While smallpox vaccine is provided free-of-charge, figures regarding the social and economic impact of orthopoxvirus infections and smallpox vaccinations are not readily available. However, rough estimates project that 40 million lives have been saved over the past 20 years as a result of smallpox eradication, and nearly $275 million saved annually in terms of quarantine

and treatment (Ullmer & Liu, 2002). Using information gained from a 2003 U.S. smallpox vaccination program, projected direct medical costs, as well as indirect costs such as wages and income lost, would likely reach $10.5 million (per million vaccinees), with upwards of 16,000 work days lost solely due to cardiac events associated with a smallpox mass vaccination campaign (Ortega-Sanchez, Sniadack, & Mootrey, 2008). While these figures are significant, the potential physical and emotional costs associated with vaccination, and orthopoxvirus infections must also be considered.

Development of Immunization Policies

While U.S. smallpox vaccination programs were discontinued in 1971 for the general public, and 1976 for healthcare workers, ACIP continued to recommend smallpox vaccinations for military personnel until 1990 (CDC, 2001). Since 1983, ACIP recommendations have been in place regarding the use of VACV vaccine to protect laboratory workers working with non-variola orthopoxviruses (CDC, 1983; CDC, 1985). These recommendations were subsequently expanded in 1984 to include persons working in animal-care areas where studies with orthopoxviruses were being conducted, and also specified the need for having documented evidence of a satisfactory smallpox vaccination within the preceding 3 years (CDC, 1991). In 1991, ACIP expanded smallpox vaccination recommendations to include health-care workers involved in clinical trials using recombinant VACV vaccines, and also amended the recommendation for revaccination for persons working with vaccinia virus, recombinant VACV, or other non-variola orthopoxviruses to every 10 years (CDC, 1991).

Due to the heightened concern regarding the potential use of VARV as an agent of bioterrorism, in 2001, ACIP developed recommendations for the non-emergency use of VACV vaccine among laboratory and healthcare workers who may be occupationally exposed to

VACV, recombinant VACVs, as well as other orthopoxviruses that have potential to cause human infections (CDC, 2001). Additionally, recommendations were made regarding the use of VACV vaccine if smallpox were to be used as an agent of biological terrorism, or if a smallpox outbreak were to occur for any reason (CDC, 2001). Following the terrorist attacks in the U.S. in 2001, ACIP published a supplemental report in 2003, which provided recommendations for using smallpox vaccine in a pre-event vaccination program in the U.S. (CDC, 2003a). Though the supplemental recommendations remained unchanged for laboratory workers, they further expanded vaccination recommendations to include personnel designated as first-responders in the event of a smallpox outbreak, workers within acute-care hospital settings who may be tasked with caring for infected patients, as well as individuals administering smallpox vaccine within the pre-event vaccination program (CDC, 2003a).

Shortly after implementation of the pre-event vaccination program, CDC reported cases of cardiac adverse events among persons who had been recently vaccinated with smallpox vaccine (CDC, 2003b). In response to these reports, ACIP convened an emergency meeting to amend vaccination recommendations to exclude individuals with known underlying heart disease (both symptomatic and asymptomatic), and those known to have three or more of the following major cardiac risk factors: hypertension, diabetes, hypercholesterolemia, heart disease at age 50 in a first-degree relative, and smoking (CDC, 2003b).

Summary of Current Problem and Study Relevance

The most recent vaccination recommendations regarding smallpox vaccine were developed and approved by ACIP in 2003, and specifically state Dryvax as the vaccine to be administered (CDC, 2001; CDC, 2003a). With the last remaining stocks of Dryvax destroyed in 2008, ACAM2000 has been the only FDA licensed and available vaccine for protection against

orthopoxvirus infections in the U.S. since 2008. While the FDA has already adjudicated ACAM2000 to be a suitable replacement for Dryvax, ACIP recommendations have not been amended to reflect the use of ACAM2000 in smallpox vaccination programs. Therefore, there is an immediate need for the development and implementation of vaccination recommendations to reflect the current use of ACAM2000 as the smallpox vaccine utilized in the U.S. to protect individuals who are at risk for orthopoxvirus disease. With the adoption of the GRADE framework for developing evidence-based recommendations by ACIP in 2010, development of ACAM2000 vaccination recommendations will require applying the GRADE approach. As this will be the first time an orthopoxvirus vaccine has undergone a stringent evidence-based evaluation for the development of vaccination recommendations, assessing the quality of the evidence in this manner will highlight the strengths, limitations, and overall applicability of this approach to the development of current, and future, orthopoxvirus vaccine recommendations.

CHAPTER 3
METHODOLOGY

Introduction

A mixed methods, evidence-based approach was utilized to grade the evidence for the policy question considered by the ACIP Smallpox Vaccine Workgroup: "Should ACAM2000 be recommended routinely to persons at risk for orthopoxvirus disease"? A detailed overview of the methods and materials utilized in applying the GRADE approach to this policy question are addressed within this chapter.

Methods

PICO

The population, intervention, comparison, and outcomes (PICO) of interest were determined by members of the ACIP Smallpox Vaccine Workgroup. The population (P) of interest was identified as those persons at risk for orthopoxvirus disease due to their occupation and/or possible exposure to orthopoxviruses. The intervention (I) vaccine for this study was ACAM2000, while the comparison (C) vaccine was Dryvax. The specific outcomes (O) of interest were determined by the Workgroup as described below.

Rating of Outcome Measures and Modified Delphi Analysis

Input regarding those health outcomes commonly associated with smallpox vaccination was solicited in order to identify outcomes (harms and benefits) the Workgroup felt were most important and should be included when examining the evidence for addressing the policy question of interest. A rating form was distributed to the Workgroup for consideration, and outcomes of interest were determined via a modified Delphi analysis. Members were asked to rate each outcome on a 9-point scale on whether the outcome should be considered: not

important (1-3), important (4-6), or critical (7-9) when making vaccination recommendations, as well as, whether or not the health outcome should, or should not, be included in the evidence evaluation and Summary of Findings (SOF) table. Results of the outcome rating were compiled and analyzed accordingly. A copy of the form distributed to the Workgroup for rating of outcome measures is presented in Appendix A.

Literature Review

A literature review was conducted by searching the PubMed electronic database for articles, data, and information written in English that were published through August 22, 2013. The objective of this literature review was to identify secondary data sources directly relevant to the PICO policy question. Specifically, those data sources which provided a direct comparison of smallpox vaccines ACAM2000 and Dryvax in human subjects. The titles, abstracts, and full text articles identified through the database search were then screened for inclusion. Relevant data sources were also identified through screening the reference sections of full-text articles. Details on search criteria used are included in Appendix B, while Figure 1 provides an overview of the approach taken for selection of studies included in literature review.

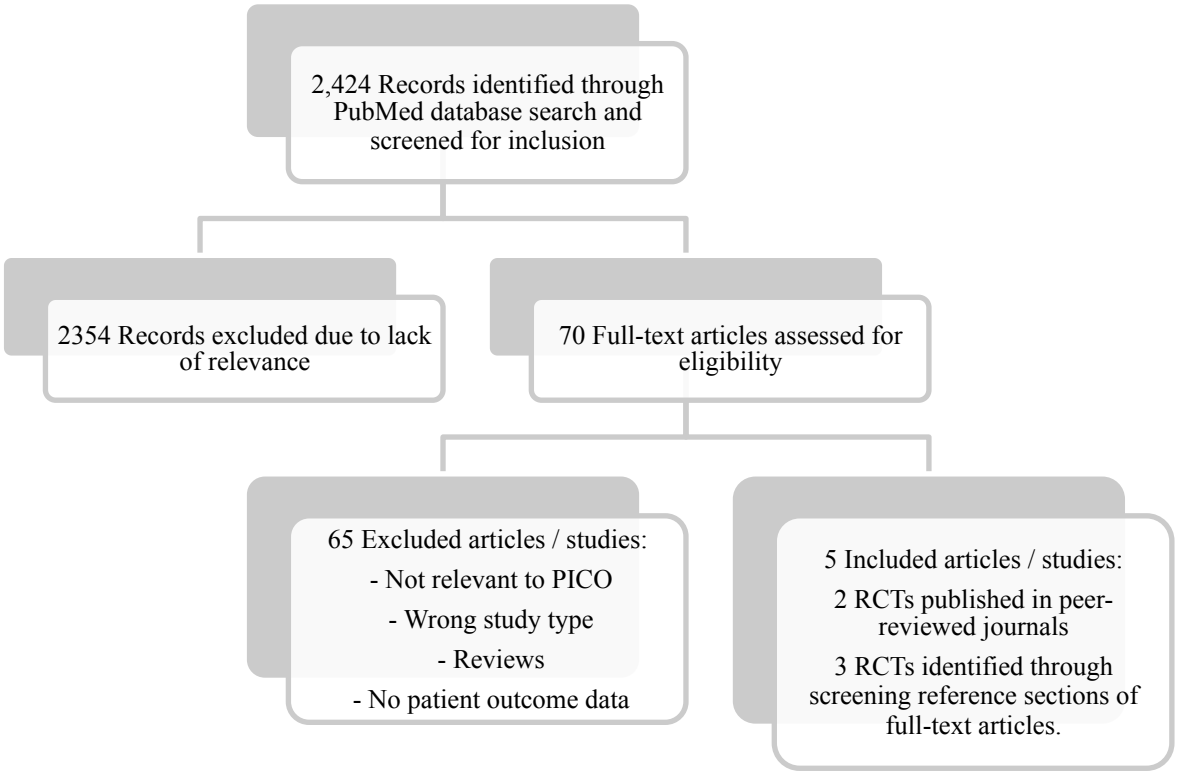

Figure 1. Overview of approach taken for selection of studies included in literature review.

Assessment of Risk of Bias

As study limitations may bias the estimates of effect of an intervention on health outcomes, an assessment of risk of bias for randomized controlled trials was conducted according to the guidelines presented within the ACIP GRADE Handbook (Ahmed, 2013). The randomized controlled trials identified through the literature review that met the PICO criteria were assessed for bias using Form 2a adapted from the ACIP GRADE Handbook (Ahmed, 2013; see Appendix C).

Data Extraction

Data for all identified outcomes were extracted from each study, specifically for those individuals within the evaluable study populations who received a dosage of ACAM2000 closest to that received by individuals vaccinated with Dryvax. Benefit outcomes were assessed and reported in all five RCTs and included both cutaneous response (vaccination success) and neutralizing antibody response (geometric mean titer, GMT) based on the 50% plaque reduction neutralization test ($PRNT_{50}$). Outcomes considered harms were assessed and reported in four out of five RCTs and included: mild adverse events (MAE), serious adverse events (SAE), myo/pericarditis resolved with sequelae, myo/pericarditis resolved without sequelae, and inadvertent inoculation. Data extracted for all outcomes were compiled into Evidence Tables and a Summary of Findings Table.

Effect Estimates

Effect estimates were generated using RevMan software (Review Manager, 2008) and are presented as Forest Plots. Pooled risk ratios (relative risk) were calculated for those outcomes of interest across all RCTs, that had been measured and for which data was available, using an inverse variance statistical method and random effects analysis model.

Grading Evidence Type (Quality)

The type (quality) of evidence for each outcome was determined based on the studies reviewed and the criteria outlined in Form 4 of the ACIP GRADE Handbook (Ahmed, 2013; Appendix D). The evidence type was initially classified based on study design. As per the ACIP GRADE handbook, evidence should be classified as Type 1 (high quality) for randomized controlled trials (RCTs) (Ahmed, 2013; Balsham *et al.*, 2011)). Randomized controlled trials with important limitations, or observational studies that exhibit exceptionally strong evidence should be classified as Type 2 (moderate quality), while initial evidence type should be

considered Type 3 (low quality) for observational studies (Ahmed, 2013; Balsham *et al*., 2011). Finally, clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations should be classified as Type 4 (very low quality) (Ahmed, 2013; Balsham *et al*., 2011). Evidence type may be downgraded if any of the GRADE criteria concerning: risk of bias, inconsistency, indirectness, imprecision, and publication bias are determined to be serious (-1) or very serious (-2) (Ahmed, 2013; Balsham *et al*., 2011). Alternatively, evidence type may also be upgraded if a large magnitude of effect exists, when there is a dose-response gradient, and when there is no serious risk of bias present. In these instances, the evidence would be rated up for strong (+1), or very strong (+2) associations (Ahmed, 2013; Balsham *et al*., 2011). Once the evidence type for each outcome was determined, findings for all outcomes were compiled into a Summary of Findings Table, and the overall evidence type across all critical outcomes was subsequently determined from the lowest evidence quality of the critical outcomes assessed.

Data Analysis

Data extracted from studies for the health outcomes of interest were analyzed and included in the evidence evaluation. Computed pooled risk ratios (relative risk and mean difference) across studies were generated using RevMan meta-analysis software and presented as Forest Plots. Confidence intervals (95% CI) were calculated using variance data available from Phase 3 studies and subsequently applied to the Phase 1 and Phase 2 studies lacking variance data. Data for GMT were converted to a log scale for computing pooled estimates prior to analysis in RevMan. The calculated pooled GMT ratio and 95% CI were then converted back to their original metrics by taking their exponentials (anti-log). Finally, reported rates of SAE were

used to calculate the percent chance you would not see a specific SAE within the included studies, as well as the sample size needed to detect twice the adverse event rate.

Study Limitations and Delimitations

When conducting smallpox vaccine research on human subjects, researchers are met with several limitations, which have a direct impact on the data available for analysis within this study. First, due to the inability to conduct viral challenges in humans, we are left to substitute cutaneous response (vaccination success or "take") as a correlate of protection. Furthermore, as these studies are directly comparing two smallpox vaccines, there is no true "control" (placebo) for these studies. Additionally, while the number of randomized controlled trials included within this analysis are small, the sample size within these studies is also small, therefore reducing the chance of observing the true rate of adverse events that may be seen in the greater population. In terms of delimitations, while the literature included in the evidence evaluation of this study included direct comparisons of Dryvax and ACAM2000, there remains a large amount of literature that may have provided useful information, yet was not considered, due to the nature of the policy question considered by the Smallpox Vaccine Workgroup.

CHAPTER 4
RESULTS

Introduction

Applying the GRADE framework to the ACAM2000 evidence considered by the ACIP Smallpox Vaccine Workgroup, and subsequently moving from evidence to recommendations, is a multi-step approach. Formulating the PICO, identifying outcomes of interest, summarizing the evidence, and determining the evidence type (quality) for each outcome, as well as the overall evidence type across all outcomes are all involved in this evidence-based approach. This chapter presents the results of the study objectives and provides an analysis of the data used to determine the overall evidence type for ACAM2000 in the context of the PICO.

Findings

Rating of Outcome Measures & Modified Delphi Analysis

Input regarding the rating of outcome measures was solicited via distribution of a rating form to each of the twenty-eight Workgroup members, with responses acquired from 13 individuals, resulting in a response rate of 46.4%. Results of the outcome ratings are presented in Table 1 below. Outcomes are ranked in order of importance as determined by the Workgroup members. Outcomes with importance ratings of 1-3 are generally considered not important and are not included in the evidence tables; ratings of 4-6 are considered important but not critical for decision-making; while ratings of 7-9 are critical for decision-making and are included in the evidence tables. As per the ACIP GRADE Handbook evidence tables are generally limited to seven outcomes, and therefore a combination of critical and/or critical but not important outcomes may be considered (Ahmed, 2013).

The Workgroup identified both critical and important outcomes, however, after discussion, it was determined that all of the rated outcomes should be assessed and considered when making their recommendation. Therefore, in order to keep the number of total outcomes assessed to seven, the Workgroup decided to combine outcomes that are normally classified as serious adverse events SAE into a single category, and included: death, postvaccinial encephalitis, eczema vaccinatum, progressive vaccinia, and generalized vaccinia. Additionally, injection site reactions, as well as, those adverse events not previously identified as SAE, inadvertent inoculation, or incidences of myo/pericarditis resolved with or without sequelae were categorized as MAE.

Table 1. Rating of Outcome Measures

Outcome	Mean Importance Rating (Range)	Standard Error of Importance Rating	Include in Evidence Table?
1. Death	8.3 (6-9)	0.29	Yes
2. Postvaccinial encephalitis	7.5 (4-9)	0.35	Yes
3. Eczema vaccinatum	7.4 (4-9)	0.38	Yes
4. Myo/pericarditis resolved with sequelae	7.3 (4-9)	0.41	Yes
5. Progressive vaccinia	7.2 (4-9)	0.36	Yes
6. Cutaneous response	6.1 (2-9)	0.72	Yes
7. Generalized vaccinia	5.8 (1-9)	0.74	Yes
8. Inadvertent inoculation	5.6 (2-9)	0.71	Yes
9. Myo/pericarditis resolve without sequelae	5.5 (1-9)	0.61	Yes
10. Neutralizing antibody response	5.4 (1-9)	0.72	Yes
11. Mild adverse events / injection site reactions	4.2 (1-9)	0.79	Yes

Literature Review: Selected Studies

A search of PubMed database identified 2424 records for consideration. Additional studies were identified via scanning references of included studies and relevant reviews. Those RCTs that provided a direct analysis of the intervention (ACAM2000) and comparison (Dryvax)

vaccines were selected. No observational studies were found which provided a direct analysis of the intervention and comparison. Two Workgroup members served as reviewers and selected studies in two stages: an initial review of titles and abstracts, followed by a review of full-text articles. Studies not directly relevant to the PICO were eliminated and included a variety of records and studies involving: animals, primary molecular investigation, vaccines not of direct interest, reviews, position papers, issue briefs, and meeting notes. Any discrepancies on study selection were resolved through discussion between the reviewers. The review of literature resulted in the identification of 5 studies that fit the PICO, and were subsequently included in this study and corresponding analysis. Table 2 identifies the characteristics of the selected studies, as well as a brief description of the purpose and findings of each.

Table 2. Characteristics of Selected Studies.

Author & Publication Year	Study Design (study #)	Study Centers (N)	Subjects Enrolled (N)	Age & Vaccination Status	Reported Outcomes of Interest	Summary of Study Purpose and Findings
Frey *et al*., 2009	Phase 1 RCT (H-400-002)	1	90	18-29 y/o naïve adults	Cutaneous response, Neutralizing antibody response, MAE, SAE	To conduct a direct comparison of the safety and immunogenicity of ACAM1000, ACAM2000, and Dryvax administered at a standard titer of 1.0 x 10^8 pfu/ml in healthy vaccinia-naïve adults. Safety and immunogenicity profiles were similar. ACAM1000 and ACAM2000 were determined to be non-inferior to Dryvax.
Artenstein *et al*., 2005	Phase 2 RCT (H-400-005)	4	353	18-29 y/o naïve adults	Cutaneous response, Neutralizing antibody response, MAE, SAE	To evaluate and compare the safety, reactogenicity, and immunogenicity of ACAM2000 and Dryvax, and determine the minimum dose of ACAM2000 required to produce a successful vaccination in naïve adults. The study confirmed ACAM200 is generally safe and well tolerated in healthy, primary vaccines. Vaccination succes rates and immunogenicity of ACAM2000 were equivalent to Dryvax at a dose of approximately 10^8 pfu/mL.
Acambis Inc., 2007	Phase 2 RCT (H-400-003)	3	357	≥ 28 y/o previously vaccinated adults	Cutaneous response, Neutralizing antibody response	To evaluate the safety, tolerability and immunogenicity of four dose levels of ACAM2000 versus Dryvax in previously vaccinated adults. Vaccination with the highest ACAM2000 dose group (6.7 x 10^7 pfu/mL) was not equivalent to Dryvax wi respect to revaccination success (as determined by cutaneous response) or geometric mean titer (GMT).
Acambis Inc., 2007	Phase 3 RCT (H-400-009)	69	1162	18-29 y/o naïve adults	Cutaneous response, Neutralizing antibody response, MAE, SAE	Efficacy of ACAM2000 and Dryvax were evaluated and compared in a vaccinia-naï population. With regard to efficacy, ACAM2000 was shown to be non-inferior to Dryvax for vaccination success and GMT. There was no significant difference between ACAM2000 and Dryvax groups with regard to the overall incidence of adverse events.
Acambis Inc., 2007	Phase 3 RCT (H-400-012)	70	1819	≥ 31 y/o previously vaccinated adults	Cutaneous response, Neutralizing antibody response, MAE, SAE	Efficacy of ACAM2000 and Dryvax were evaluated and compared in a previously vaccinated population. In terms of efficacy, ACAM2000 was shown to be inferior to Dryvax with regard to revaccination success, and was shown to be non-inferior to Dryvax with regard to GMT on Day 30. In terms of safety, the incidence of adverse events was higher in the Dryvax group than in the ACAM2000 group.

Assessment of Risk of Bias

Criteria for assessing risk of bias for RCTs included adequate: allocation of sequence generation, allocation sequence concealment, blinding of participants and personnel, and blinding of outcome assessors. Additionally, each study was assessed for whether incomplete data was addressed, whether the study was free of selective outcome reporting, and free of other biases. An assessment of risk of bias for the included studies was conducted independently by two Workgroup members and revealed there was no serious risk of bias for each of the 5 RCTs included in the analysis.

Data Extraction

Data for identified outcomes of interest that were measured and observed among both the total and evaluable populations were extracted from each study and are presented in evidence tables (Tables 3 and 4). Benefit outcomes were assessed and reported in all five RCTs and included both cutaneous response (vaccination success), and neutralizing antibody response based on a $PRNT_{50}$ (and reported as GMT) (Table 3). Outcomes considered harms were assessed and reported in four out of five RCTs and included: MAE, SAE, myo/pericarditis resolved with sequelae, myo/pericarditis resolved without sequelae, and inadvertent inoculation (Table 4). Three of the studies involved vaccinia-naïve subjects (H-400-002, H-400-005, and H-400-009), while two studies were conducted on previously vaccinated subjects (H-400-003, and H-400-012). Data from study H-400-003 was not utilized in the assessment of harms within previously vaccinated individuals, due to adverse events having not been reported within the study, despite the fact that study subjects were most likely monitored for these outcomes.

An analysis of the evaluable populations revealed the cutaneous response (vaccination success) rate in vaccinia-naïve subjects was 96.6% for individuals vaccinated with ACAM2000,

and 99.4% for individuals vaccinated with Dryvax (Table 3). In study subjects who had been previously vaccinated, 84.1% of individuals vaccinated with ACAM2000 had a cutaneous response indicating a successful vaccination, compared to 98.4% of individuals vaccinated with Dryvax (Table 3). While this difference in vaccination "take" among previously vaccinated individuals is large, it is important to remember that cutaneous response, despite being recognized as the primary correlate for immunity with smallpox vaccines, must also be considered alongside neutralizing antibody titers.

Table 3. Evidence Table for Critical Outcomes: Benefits

	Study Population / Treatment Group			
	Vaccinia-Naïve Subjects		**Previously Vaccinated Subjects**	
	ACAM2000	**Dryvax**	**ACAM2000**	**Dryvax**
Cutaneous Response (Vaccination Success)				
No. of Evaluable Subjects (# studies)	857 (3)	336 (3)	1238 (2)	440 (2)
Number of Vaccination / Re-vaccination Successes (%)	828 (96.6%)	334 (99.4%)	1041 (84.1%)	433 (98.4%)
Neutralizing Antibody Response				
No. of Evaluable Subjects (# studies)	646 (3)	269 (3)	784 (2)	428 (2)
Pooled Geometric Mean Titer (GMT) Ratio[1, 2] (95% CI of pooled GMT Ratio)	0.677 (0.625 – 0.733)			

[1] Pooled GMT Ratio was generated in RevMan and was based on the evaluable subjects within the selected studies.
[2] Variance data available for Phase 3 studies was applied to the Phase 1 and 2 studies lacking variance data.

In terms of those outcomes considered harms, vaccinia-naïve subjects experienced MAE at nearly identical rates: 99.05% for ACAM2000, and 100% for Dryvax, respectively (Table 4). In previously vaccinated subjects, 96.4% of individuals who were vaccinated with ACAM2000,

experienced MAE, versus 98.8% who were vaccinated with Dryvax (Table 4). There were no cases of inadvertent inoculation reported in the studies considered.

All reported cases of myo/pericarditis were reported among vaccinia-naïve subjects and occurred in both ACAM2000 and Dryvax vaccinated individuals (Table 4). Two cases of myo/pericarditis were reported having resolved with sequelae: one vaccinia-naïve individual who had received ACAM2000 (0.10% of the study population), and one individual who had received Dryvax (0.27% of the study population). The vaccinia-naïve individual vaccinated with Dryvax, from study H-400-009, had been categorized as an "ongoing case" of myo/pericarditis within the published study report with no further information regarding long-term monitoring (Acambis Inc., 2007). However, for the purposes of this study, that subject is included within Table 4 as having myo/pericarditis resolved with sequelae. There were a total of eight cases of myo/pericarditis within the vaccinia-naïve subjects that were considered to have resolved without sequelae (Table 4). Six of those vaccinia-naïve individuals had received ACAM2000 (0.63% of the study population), with the remaining two having received Dryvax (0.54% of the study population).

In terms of SAE, one case of generalized vaccinia was reported in a previously vaccinated subject who had received Dryvax vaccine within study H-400-012. Though not included in the VRBPAC Briefing Document (Acambis Inc., 2007), this SAE was reported in the VRBPAC Background Document (Rosenthal, Merchlinsky, & Chowdhury, 2007). This SAE (Table 4; 0.22% of the study population) was discovered upon the study subject reporting to a scheduled study center visit on Day 10 post vaccination. The individual was admitted to a local hospital for observation, dermatological consult, as well as treatment, and subsequently

discharged from the hospital the following day. The SAE was determined to be study-vaccine related and resolved without sequelae on Day 13.

Table 4. Evidence Table for Critical Outcomes: Harms

	Evaluated Study Population / Treatment Group			
	Vaccinia-Naïve Subjects		**Previously Vaccinated Subjects**	
	ACAM2000 N[1] = 954 n (%) [# Studies]	**Dryvax N[1] = 368 n (%) [# Studies]**	**ACAM2000 N[1] = 1371 n (%) [# Studies]**	**Dryvax N[1] = 448 n (%) [# Studies]**
Experienced Serious Adverse Events	0 (0%) [3]	0 (0%) [3]	0 (0%) [1]	1 (.22%) [1]
Myo/pericarditis Resolved with Sequelae	1 (.10%) [3]	1 (.27%) [3]	0 (0%) [1]	0 (0%) [1]
Myo/pericarditis Resolved without Sequelae	6 (.63%) [3]	2 (.54%) [3]	0 (0%) [1]	0 (0%) [1]
Inadvertent Inoculation	0 (0%) [3]	0 (0%) [3]	0 (0%) [1]	0 (0%) [1]
Mild Adverse Events	945 (99.05%) [3]	368 (100%) [3]	1325 (96.64%) [1]	443 (98.8%) [1]

[1]Number indicated represents the total number of subjects enrolled in studies where subjects were administered either ACAM2000 or Dryvax, and subsequently monitored for the outcome(s) of interest, and results were reported.

Effect Estimates

Effect estimates for evaluable populations were generated using RevMan software (Review Manager, 2008) and presented as Forest Plots (Appendix F). A risk ratio (RR) equal to one (RR = 1) indicates no difference in the risk of the outcome of interest between ACAM2000 (experimental) and Dryvax (control) vaccines, while a risk ratio less than one (RR<1) indicates the outcome of interest is less likely to occur in ACAM2000 vaccinated individuals than those vaccinated with Dryvax. Conversely, a risk ratio greater than one (RR>1) indicates the outcome

of interest is more likely to occur in ACAM2000 vaccinated individuals than in individuals vaccinated with Dryvax.

The pooled risk ratio for the benefit outcome cutaneous response was 0.94 [95% CI: 0.80, 1.01] (Appendix F, Plot A), while the pooled mean difference for neutralizing antibody response (GMT) was 0.677 [95% CI: 0.625, 0.733] (Appendix F, Plot B). The pooled risk ratio for the harms outcome SAE was 0.11 [95% CI: 0.00, 2.67], while the pooled risk ratio for MAE was 0.99 [95% CI: 0.98, 1.00] (Appendix F; Plots C and D, respectively). In looking at the pooled risk ratios for myo/pericarditis outcomes, myo/pericarditis resolved with sequelae had a pooled risk ratio of 0.33 [95% CI: 0.02, 5.28], while the pooled risk ratio for myo/pericarditis resolved without sequelae was 1.14 [95% CI: 0.29, 4.39] (Appendix F, Plots E and F, respectively). A pooled risk ratio could not be estimated for the harms outcome inadvertent inoculation as no incidences of this outcome were reported within the selected studies.

As the pooled risk ratios for cutaneous response and MAE were close to 1, for the purposes of this study, we will conclude there to be no difference between ACAM2000 and Dryvax for these outcomes. However, the outcomes SAE and myo/pericarditis resolved with sequelae both were less likely to be seen in ACAM2000 vaccinated individuals, while myo/pericarditis resolved without sequelae was more likely to be seen in individuals vaccinated with ACAM2000, though only slightly.

Forest Plots generated in RevMan provide a graphical representation of the calculated estimate effects. Examination of the plots show there to be no difference between ACAM2000 and Dryvax in terms of cutaneous response, neutralizing antibody response (GMT), or MAE outcomes, (Appendix F, Plots A, B, and D respectively). Forest Plots for the outcomes SAE and

myo/pericarditis resolved with sequelae favor ACAM2000, while the plot for myo/pericarditis resolved without sequelae favors Dryvax.

Determining Evidence Type (Quality)

The type (quality) of evidence for each of the identified outcomes within the selected studies was determined by two members of the ACIP Smallpox Vaccine Workgroup (Table 5). As all studies considered within the analysis were RCTs the evidence type for each outcome began as evidence Type 1 (high quality) and was subsequently downgraded if, when the evidence was analyzed according to the criteria for grading, it was determined necessary.

For the purpose of this study, the benefit outcomes cutaneous response, and neutralizing antibody response, were utilized as surrogates for the outcome of primary interest: vaccine efficacy to prevent orthopoxvirus disease. Therefore, as these identified outcomes differ from the outcome in which we are interested (vaccine efficacy), the Workgroup members determined indirectness to be a serious issue, and thus downgraded the evidence one level to Type 2. All other criteria on which the benefit outcomes were analyzed were found to have no serious impact on the quality of the evidence.

The evidence analyzed for the outcomes considered to be harms including myo/pericarditis resolved with sequelae, as well as MAE, provided no reason for the downgrading of evidence quality based on the criteria considered, and thus remained Type 1. As the clinical relevance of myo/pericarditis resolved without sequelae is unclear, indirectness was determined to have an impact on evidence quality, and thus was downgraded to Type 2. In regards to SAE and inadvertent inoculation, evidence type was downgraded to Type 2 due to imprecision, as the studies analyzed were not powered to detect these outcomes. Table 1 in Appendix E illustrates the rates of serious adverse events often seen as a result of smallpox vaccination, and provides the required sample size needed within a study population in order to

detect twice the adverse event rate. These rates further illustrate that the populations within the studies analyzed were significantly smaller than the population size needed to detect these rare adverse events.

When determining the overall evidence type across all critical outcomes, the lowest evidence type for any of the critical outcomes considered determines the overall evidence type. As the evidence type for the critical outcomes considered was either Type 1 or Type 2, the overall evidence type across all critical outcomes was therefore determined to be Type 2 (moderate quality).

Table 5. Summary of Findings Table: Evidence Type (Quality) for ACAM2000

Outcome	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision[4]	Other considerations[1]	Evidence Type (Quality)
Benefits							
Cutaneous Response	RCT (5)	No Serious	No Serious	Serious[2]	No Serious	None	2 (Moderate)
Neutralizing Antibody Response	RCT (5)	No Serious	No Serious	Serious[2]	No Serious	None	2 (Moderate)
Harms							
Serious Adverse Events	RCT (4)	No Serious	No Serious	No Serious	Serious[4]	None	2 (Moderate)
Myo/pericarditis Resolved with Sequelae	RCT (4)	No Serious	No Serious	No Serious	No Serious	None	1 (High)
Myo/pericarditis Resolved without Sequelae	RCT (4)	No Serious	No Serious	Serious[3]	No Serious	None	2 (Moderate)
Inadvertent Inoculation	RCT (4)	No Serious	No Serious	No Serious	Serious[4]	None	2 (Moderate)
Mild Adverse Events	RCT (4)	No Serious	No Serious	No Serious	No Serious	None	1 (High)
Overall evidence type across all critical outcomes (Quality)	**2 (Moderate)**						

[1]Strength of association, dose-response, opposing plausible residual confounding or bias, publication bias.

[2]Cutaneous response and neutralizing antibody response were surrogates for the outcome of primary interest: vaccine efficacy to prevent orthopoxvirus disease
[3]The clinical significance of myo/pericarditis resolved without sequelae is unclear; therefore, myo/pericarditis resolved with sequelae was assessed to be the outcome of interest.
[4] The total number of participants enrolled across all RCTs was <4000. Thus, these studies were not powered to detect serious adverse events (i.e. EV, PV, PVE, death) or inadvertent inoculation. Please see Appendix E for information regarding sample size needed to detect twice the AE rate.

Summary

To determine the overall evidence type (quality), the body of evidence was evaluated across all critical outcomes utilizing data extracted from five RCTs, identified through a systematic review of literature, that were directly relevant to the policy question and met the PICO criteria. A summary of all relevant evidence for critical outcomes was presented, and the quality of evidence for each outcome was determined. Pooled risk ratios were calculated and showed no clear difference between ACAM2000 and Dryvax vaccines for the outcomes MAE and cutaneous response. Risk ratios calculated for outcomes SAE, and myo/pericarditis resolved with sequelae, indicated these outcomes were less likely to be seen in ACAM2000 vaccinated individuals than in individuals vaccinated with Dryvax. However, myo/pericarditis resolved without sequelae was more likely to be seen in ACAM20000 vaccinated individuals than in those vaccinated with Dryvax.

As RCTs were used, the initial evidence type was determined to be Type 1 for each critical outcome. However, evidence analyzed showed the need to rate down the quality of evidence for the cutaneous response, neutralizing antibody response, as well as myo/pericarditis resolved without sequelae outcomes due to indirectness. Thus, the evidence type for these critical outcomes was determined to be Type 2. Evidence quality was also rated down for the outcomes serious adverse events and inadvertent inoculation due to imprecision, and as such, was also determined to be evidence Type 2. Despite two critical outcomes having been graded as Type 1,

the overall evidence type is determined from the lowest quality evidence across all critical outcomes, therefore the overall evidence type was determined to be Type 2.

CHAPTER 5
CONCLUSIONS, IMPLICATIONS, and RECOMMENDATIONS

Introduction

In this study, evidence obtained from randomized controlled trials, identified through a systematic review of literature, was evaluated using the GRADE approach, a framework for developing evidence-based recommendations. The evaluated evidence will be used in the development of ACIP recommendations addressing the policy question whether ACAM2000 should be routinely recommended for persons at risk for orthopoxvirus disease. This chapter provides a summary of the study, discusses the findings, and conclusions. Additionally, the implications of this project on guiding the development of current and future public health policies, specifically, as they pertain to smallpox vaccination recommendations, will be discussed.

Summary of Study

Despite the eradication of smallpox, the potential for acquiring orthopoxvirus disease still exists. As of 2008, when use of Dryvax was discontinued, ACAM2000 became the only FDA licensed and approved smallpox vaccine available for use in the U.S. However, current ACIP smallpox vaccination recommendations have not been updated to reflect the adoption of ACAM2000 as the sole vaccine available. As the current recommendations are out of date, the need to develop new ACIP smallpox vaccination recommendations is paramount. However, development of new recommendations requires utilizing the GRADE approach, the ACIP adopted framework for developing evidence-based recommendations. The purpose of this study was to evaluate ACAM2000 according to the GRADE framework in order to provide the ACIP Smallpox Vaccine Workgroup with a thorough evidence-based analysis of the benefits and

harms associated with ACAM2000. This analysis will be utilized to help guide the development of new ACIP smallpox vaccination recommendations for ACAM2000.

The ACIP Smallpox Vaccine Workgroup established the policy question: "Should administration of ACAM2000 be recommended routinely to persons at risk for orthopoxvirus disease", and identified those outcomes determined to be critical in making recommendations for the policy question. Seven critical outcomes were identified by the Workgroup through a modified Delphi Analysis; two were benefits (cutaneous response, and neutralizing antibody response), while five were harms (serious adverse events, myo/pericarditis resolved with sequelae, myo/pericarditis resolved without sequelae, inadvertent inoculation, and mild adverse events).

After conducting a systematic review of literature, five studies were identified that met the criteria established based on the policy question. Data were extracted from each study and analyzed accordingly. Pooled estimate effects (risk ratio and mean difference) were calculated and Forest Plots were generated. Risk ratios for cutaneous response and MAE indicated there was no difference in these outcomes occurring in individuals vaccinated with ACAM2000 or Dryvax, while SAE and myo/pericarditis resolved with sequelae were each less likely to occur in those vaccinated with ACAM2000. However, myo/pericarditis resolved without sequelae was more likely to occur among individuals vaccinated with ACAM2000 than those vaccinated with Dryvax.

When determining the evidence type for each critical outcome, as all studies analyzed were RCTs, the evidence type for each critical outcome was initially graded as Type 1. However, both benefit outcomes were downgraded to evidence Type 2 due to serious indirectness, as these outcomes were considered surrogates for the primary outcome of interest: vaccine efficacy to

prevent orthopoxvirus disease. Similarly, the outcome myo/pericarditis resolved without sequelae was also downgraded to evidence Type 2 due to indirectness as the clinical significance of the outcome was determined to be unclear. The harms outcomes, SAE and inadvertent inoculation, were downgraded to evidence Type 2 due to imprecision. This downgrade was based on the fact that the studies analyzed were not powered to detect these critical outcomes. The remaining outcomes, myo/pericarditis resolved with sequelae and MAE, were not downgraded and remained evidence Type 1. Finally, the overall evidence type across all critical outcomes was then determined based on the lowest evidence quality from the critical outcomes assessed, and was determined to be Type 2.

Conclusions

Despite having applied the rigorous evidence-based GRADE approach in the grading of evidence quality for ACAM2000, there are still numerous factors to consider when formulating vaccination recommendations. Though the overall evidence type was determined to be Type 2 (moderate quality), the impact this assessment has on the wording and development of vaccination recommendations remains to be seen. Assessing the evidence quality of ACAM2000 using GRADE ultimately is a subjective process and does not eliminate the need for, or minimize the importance of, professional judgment by orthopoxvirus, and smallpox vaccine, subject matter experts. Additionally, utilizing GRADE does not imply that quality of evidence can solely be objectively determined, nor does it eliminate the possibility of disagreements among Smallpox Vaccine Workgroup members in interpreting evidence or deciding on the best courses of action.

While the aim of the ACIP GRADE framework is to provide an evidence-based systematic approach for the development of recommendations, this was but one step in that process. The next steps involve careful consideration of the evidence analyzed within this study,

and formulation of the wording, as well as determination of the category of the recommendations by the Smallpox Vaccine Workgroup. This will require the Workgroup to look at the issue of vaccination from the perspective of the vaccinees, which is not easily quantifiable. In this regard, several components of the Health Belief Model (HBM) will be considered in decision-making. The HBM theorizes that an individual's belief regarding their susceptibility to a disease, as well as their perceptions of the benefits of trying to avoid the disease, ultimately influence their readiness to act (Rimer & Glanz, 2005). With health motivation as its central focus, the HBM is comprised of six concepts, which provide a framework for designing short and long-term behavior change strategies (Rimer & Glanz, 2005). By considering the six concepts of the HBM when applying the GRADE approach to developing smallpox vaccination recommendations, the Smallpox Vaccine Workgroup will aim for a greater understanding of the target population and their perceived susceptibility to orthopoxvirus infections; whether the target population believes possible orthopoxvirus infections are of serious health concern; and whether they believe vaccination can reduce the threat of orthoxpoxvirus infection at an acceptable cost (Rimer & Glanz, 2005). Likely, these same considerations will be weighed by potential vaccinees themselves, and hopefully, will influence their decision to undergo vaccination with ACAM2000 according to the recommendations developed by the Smallpox Vaccine Workgroup.

Implications and Recommendations

The information provided as a result of this study will be made available to the ACIP Smallpox Vaccine Workgroup and will be presented, along with the smallpox vaccination recommendations, once developed, to ACIP for final consideration. Ultimately, the results of this study will help to inform those in charge of making U.S. public health policy regarding smallpox vaccinations for persons at risk for orthopoxvirus disease.

Despite the FDA having already adjudicated the ACAM2000 clinical trial data, and subsequently approved the vaccine for license and use within the U.S., the process undertaken in this study is a proof of concept, and can be seen as an exercise in completing the requirements necessary for ACIP consideration. While the importance of an evidence-based systematic approach, and the need to bring transparency to the development of recommendations cannot be disputed, the ACIP GRADE framework is not a one-size-fits all approach, and the process presented within this study had several elements that warrant further consideration.

First, when addressing policy questions, and developing recommendations for vaccines or interventions where the numbers of studies are limited, or are small in sample size, as was the case with ACAM2000, applying GRADE to arrive at implicit conclusions regarding those outcomes of interest that are rare, can prove difficult. Second, as with any study, evidence analysis is only as good as the evidence (data) available. The evidence examined within this study was often found to be inconsistent or incomplete. As variance data for neutralizing antibody response was not provided for each study, the need to apply the variance from Phase 3 studies, to the considerably smaller Phase 1 and Phase 2 studies, likely resulted in over-estimated confidence intervals, and therefore most likely impacted the calculated pooled GMT ratio. Finally, pooling data from different clinical trial phases that were considerably different in size, which also included two distinct populations of individuals (naïve vs. previously vaccinated) that were unevenly represented within each study, adds an element of uncertainty to the calculated risk ratios.

Despite these factors, the overall evidence type for ACAM2000 was determined. In addition to the evidence type, the Smallpox Vaccine Workgroup will also need to consider the social costs of vaccination, contraindications to vaccination, as well as the potential impact of the

harms outcomes identified within this study when formulating their recommendations. To that end, the evidence extracted, and summarized, from the included studies will certainly aid in their informed decision-making on this important public health issue.

While the need for development of evidence-based recommendations is important, re-evaluating evidence that has previously been adjudicated by a Government regulatory agency may be seen as redundant. Initially, consideration was given to potentially identifying alternative frameworks or approaches that may have been better alternatives to GRADE for use in the development of vaccination recommendations for future smallpox vaccines. However, after conducting this study, despite the drawbacks previously identified, GRADE has proven to be a useful and informative, albeit resource intensive, approach to critically evaluating the evidence for ACAM2000. Using the GRADE approach actually helped to highlight the lack of robustness in data available for ACAM2000. That being said, through applying GRADE, one can be sure the recommendations developed will not only be evidence-based, but will be based on a very thorough analysis of the best evidence available. Therefore, as a result of this study and its findings, it is recommended that ACIP continue to utilize GRADE in the development of vaccination recommendations. However, consideration should be given to perhaps providing alternatives, or modifications, in instances where data is not robust, and therefore does not easily "fit" within the components of the analysis framework, as was the case with ACAM2000. In the end, regardless of the data available, or evidence type determined, ample emphasis should always be placed on the informed decisions and opinions of subject matter experts, which guide the development of evidence-based recommendations to achieve the desired public health goal.

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APPENDIX A: RATING OF OUTCOME MEASURES

ACIP Smallpox Vaccine Workgroup

Input from Workgroup members is requested regarding the rating of outcome measures in order to determine those outcomes that should be included in evidence evaluation.

Policy question

Should administration of ACAM2000® be recommended routinely to persons at risk for Orthopoxvirus disease?

Rating outcome measures to be evaluated

Please rate the relative importance of each outcome measure for developing recommendations on the routine administration of ACAM2000 to persons at risk for Orthopoxviral disease.

Please assign a single number to rate **each** of the outcome measures in the table below. Assign a rating regardless of whether data are available for the outcome.

Use a 9-point scale ranging from 1 (not important) to 9 (critical) using the following criteria:

- 1 – 3: **Not important**; do not include in the evidence evaluation
- 4 – 6: **Important but not critical** for making a recommendation; inclusion may depend on the number of other important or critical outcomes
- 7 – 9: **Critical** for making a recommendation; include in the evidence evaluation

Outcome	Rating
1. Neutralizing antibody response	
2. Cutaneous response	
3. Inadvertent inoculation	
4. Myo/pericarditis resolved with sequelae	
5. Myo/pericarditis resolved without sequelae	
6. Death	
7. Eczema vaccinatum	
8. Progressive vaccinia	
9. Postvaccinial encephalitis	
10. Generalized vaccinia	
11. Mild adverse events / injection site reactions	

APPENDIX B: LITERATURE REVIEW SEARCH CRITERIA

PubMed

((("smallpox vaccine" or ACAM2000 or Dryvax) AND English[lang])) OR (smallpox vaccine[MeSH Terms] AND English[lang])

APPENDIX C: ASSESSMENT OF RISK OF BIAS FOR RANDOMIZED CONTROLLED TRIALS

Form 2a. Assessment of risk of bias for randomized controlled trials

Author, Year:

Name of reviewer: Date completed:

Criteria	Description	Yes /No/ Unclear	Quote from study
Adequate allocation sequence generation	The investigators describe a random component in the sequence generation process (e.g., computer random number generator). Problem if "pseudo" or "quasi" randomization with allocation by day of week, birth date, chart number, etc.		
Adequate allocation sequence concealment	Those enrolling patients cannot foresee the group to which the next enrolled patient will be allocated (e.g., central allocation, sequentially numbered sealed envelopes)		
Adequate blinding of participants and personnel	Study participants and personnel are not aware of the arm to which patients are allocated		
Adequate blinding of outcome assessors	Outcome assessors are not aware of the arm to which patients are allocated (assess separately for each outcome; outcomes may be grouped as subjective and objective)		
Incomplete outcome data addressed	Loss to follow-up; adherence to the intention to treat principle when indicated (assess separately for each outcome; outcomes may be grouped as short-term and long-term)		
Free of selective outcome reporting	Study reports all pre-specified or expected outcomes. Problem if reporting of some outcomes and not others on the basis of the results		
Free of other biases	For example: stopping early for benefit; extreme baseline imbalance; use of unvalidated patient-reported outcomes		

APPENDIX D: DETERMINING EVIDENCE TYPE

Form 4. Determining evidence type

Name of reviewer:

Date completed:

Criteria	Assessment (circle one for each criterion)	Reasons for assessment	Evidence type[a] (Circle one per outcome)
OUTCOME:			
Risk of bias	No serious (-1) very serious (-2)		1
Inconsistency	No serious (-1) very serious (-2)		2
Indirectness	No serious (-1) very serious (-2)		3
Imprecision	No serious (-1) very serious (-2)		4
Publication bias	Unlikely likely (-1) very likely (-2)		
Strength of association	No Large (+1) Very large (+2)		
Dose response relation	No Yes (+1)		
Effects of opposing plausible residual confounding or bias	No Yes (+1)		

[a]Evidence type:

1= Randomized controlled trials (RCTs), or overwhelming evidence from observational studies.

2= RCTs with important limitations, or exceptionally strong evidence from observational studies.

3= Observational studies, or RCTs with notable limitations.

4= Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations.

APPENDIX E: REPORTED RATES OF SERIOUS ADVERSE EVENTS

	Rates of SAE in vaccinated population (# cases / million vaccinations)[1]		**% Chance You Would NOT see SAE in ACAM2000 RCTs**		**Sample Size Needed to Detect Twice the SAE Rate (Power 0.8)**	
	Naïve (n= 1207)	**Previously Vaccinated (n=1670)**	**Naïve**	**Previously Vaccinated**	**Naïve**	**Previously Vaccinated**
Eczema vaccinatum	38.5	3	95.50%	99.50%	611,565	7,848,844
Progressive vaccinia	1.5	3	99.80%	99.50%	15,697,723	7,848,844
Postvaccinial encephalitis	12.3	2	98.50%	99.60%	1,914,325	11,773,284
Inadvertent Inoculation	529.2	42.1	52.80%	95.00%	44,459	559,267
Death	1.5	NA	99.80%	NA	15,697,723	NA

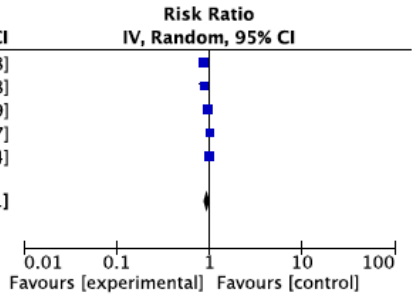
[1]Rates of SAE reported from Lane, J.M., Ruben, F.L., Neff, J.M., Millar, J.D. (1970). Complications of smallpox vaccination, 1968: results of ten statewide surveys. *Journal of Infectious Diseases*. 122 (4): 303-309.

APPENDIX F: ESTIMATE EFFECTS – FOREST PLOTS

Forest Plot A: Cutaneous Response

Study or Subgroup	ACAM2000 Events	ACAM2000 Total	Dryvax Events	Dryvax Total	Weight	Risk Ratio IV, Random, 95% CI
ACAMBIS 2007 (H400-012)	998	1189	381	388	22.2%	0.85 [0.83, 0.88]
ACAMBIS 2007 (H400-003)	43	49	52	52	14.5%	0.88 [0.79, 0.98]
ACAMBIS 2007 (H400-009)	747	776	255	257	22.7%	0.97 [0.95, 0.99]
Frey 2009 (H400-002)	30	30	30	30	19.2%	1.00 [0.94, 1.07]
Artenstein 2005(H400-005)	51	51	49	49	21.5%	1.00 [0.96, 1.04]
Total (95% CI)		**2095**		**776**	**100.0%**	**0.94 [0.88, 1.01]**
Total events	1869		767			

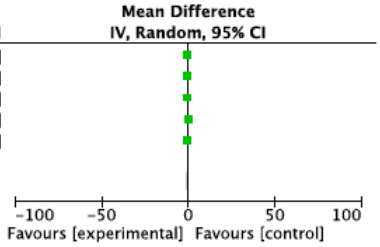
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 69.84$, df = 4 ($P < 0.00001$); $I^2 = 94\%$
Test for overall effect: Z = 1.72 (P = 0.09)



Forest Plot B: Neutralizing Antibody Response (GMT)

Study or Subgroup	ACAM2000 Mean	ACAM2000 SD	ACAM2000 Total	Dryvax Mean	Dryvax SD	Dryvax Total	Weight	Mean Difference IV, Random, 95% CI
ACAMBIS 2007 (H400-003)	5.55	0.018	50	6.1	0.0104	52	20.1%	-0.55 [-0.56, -0.54]
ACAMBIS 2007 (H400-009)	5.11	0.0321	565	5.54	0.0219	190	20.1%	-0.43 [-0.43, -0.43]
ACAMBIS 2007 (H400-012)	5.66	0.0164	734	6.1	0.0106	376	20.1%	-0.44 [-0.44, -0.44]
Artenstein 2005(H400-005)	5.04	0.0342	51	5.06	0.0346	49	20.0%	-0.02 [-0.03, -0.01]
Frey 2009 (H400-002)	4.64	0.0498	30	5.14	0.0314	30	19.8%	-0.50 [-0.52, -0.48]
Total (95% CI)			**1430**			**697**	**100.0%**	**-0.39 [-0.47, -0.31]**

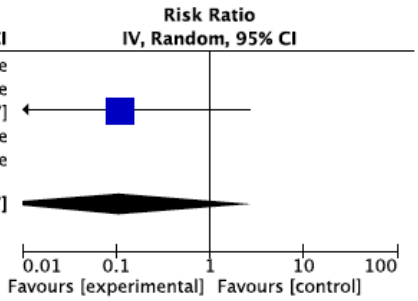
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5189.32$, df = 4 ($P < 0.00001$); $I^2 = 100\%$
Test for overall effect: Z = 9.64 ($P < 0.00001$)



Forest Plot C: Serious Adverse Events (SAE)

Study or Subgroup	ACAM2000 Events	ACAM2000 Total	Dryvax Events	Dryvax Total	Weight	Risk Ratio IV, Random, 95% CI
ACAMBIS 2007 (H400-003)	0	49	0	52		Not estimable
ACAMBIS 2007 (H400-009)	0	873	0	289		Not estimable
ACAMBIS 2007 (H400-012)	0	1371	1	448	100.0%	0.11 [0.00, 2.67]
Artenstein 2005(H400-005)	0	51	0	49		Not estimable
Frey 2009 (H400-002)	0	30	0	30		Not estimable
Total (95% CI)		**2374**		**868**	**100.0%**	**0.11 [0.00, 2.67]**
Total events	0		1			

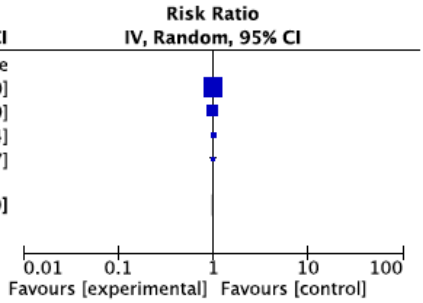
Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)



Forest Plot D: Mild Adverse Events (MAE)

Study or Subgroup	ACAM2000 Events	ACAM2000 Total	Dryvax Events	Dryvax Total	Weight	Risk Ratio IV, Random, 95% CI
ACAMBIS 2007 (H400-003)	0	49	0	52		Not estimable
ACAMBIS 2007 (H400-009)	864	873	289	289	64.7%	0.99 [0.98, 1.00]
ACAMBIS 2007 (H400-012)	1325	1371	443	448	29.3%	0.98 [0.96, 0.99]
Artenstein 2005(H400-005)	51	51	49	49	4.3%	1.00 [0.96, 1.04]
Frey 2009 (H400-002)	30	30	30	30	1.6%	1.00 [0.94, 1.07]
Total (95% CI)		**2374**		**868**	**100.0%**	**0.99 [0.98, 1.00]**
Total events	2270		811			

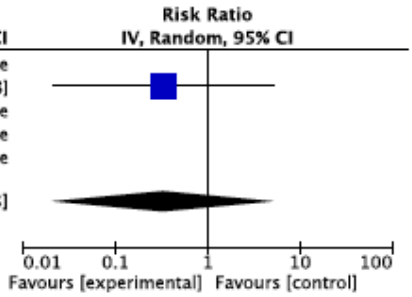
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.28$, df = 3 ($P = 0.35$); $I^2 = 8\%$
Test for overall effect: Z = 3.06 (P = 0.002)



Forest Plot E: Myo/Pericarditis Resolved With Sequelae

Study or Subgroup	ACAM2000 Events	ACAM2000 Total	Dryvax Events	Dryvax Total	Weight	Risk Ratio IV, Random, 95% CI
ACAMBIS 2007 (H400-003)	0	49	0	52		Not estimable
ACAMBIS 2007 (H400-009)	1	873	1	289	100.0%	0.33 [0.02, 5.28]
ACAMBIS 2007 (H400-012)	0	1371	0	448		Not estimable
Artenstein 2005(H400-005)	0	51	0	49		Not estimable
Frey 2009 (H400-002)	0	30	0	30		Not estimable
Total (95% CI)		**2374**		**868**	**100.0%**	**0.33 [0.02, 5.28]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.43)



Forest Plot F: Myo/Pericarditis Resolved Without Sequelae

Study or Subgroup	ACAM2000 Events	ACAM2000 Total	Dryvax Events	Dryvax Total	Weight	Risk Ratio IV, Random, 95% CI
ACAMBIS 2007 (H400-003)	0	49	0	52		Not estimable
ACAMBIS 2007 (H400-009)	4	873	2	289	63.7%	0.66 [0.12, 3.60]
ACAMBIS 2007 (H400-012)	0	1371	0	448		Not estimable
Artenstein 2005(H400-005)	1	51	0	49	18.1%	2.88 [0.12, 69.16]
Frey 2009 (H400-002)	1	30	0	30	18.2%	3.00 [0.13, 70.83]
Total (95% CI)		**2374**		**868**	**100.0%**	**1.14 [0.29, 4.39]**
Total events	6		2			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.08$, df = 2 (P = 0.58); $I^2 = 0\%$
Test for overall effect: Z = 0.19 (P = 0.85)