Vaccines: A Biography

Andrew W. Artenstein
Editor

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Editor
Andrew W. Artenstein
Department of Medicine and Community Health
Brown University
Providence, RI 02912
USA
artenstein@brown.edu

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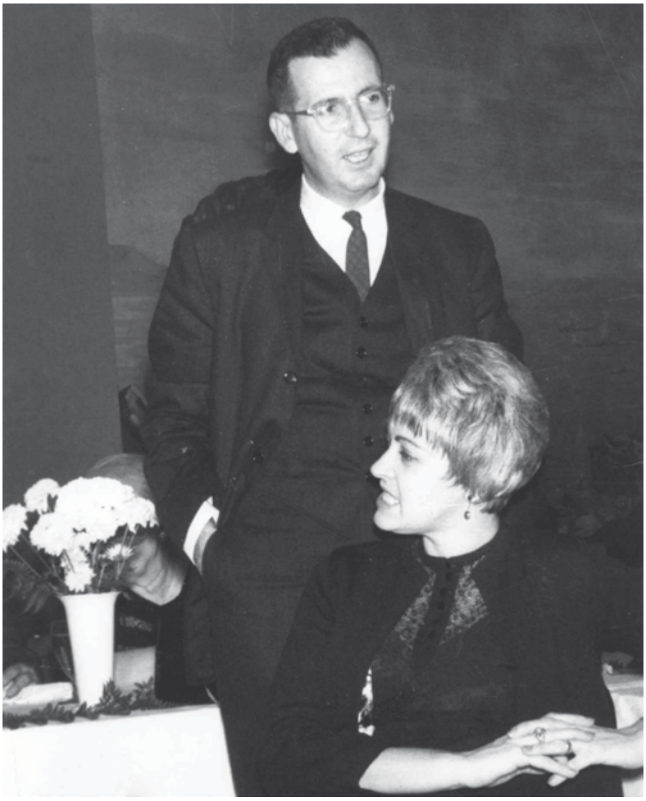
*To my parents, Malcolm (1930–1976)
and Sylvia (1933–2007), who inspired
me in countless ways. They made the story
personal.*



Preface

Why another book about vaccines? There are already a few extremely well-written medical textbooks that provide comprehensive, state-of-the-art technical reviews regarding vaccine science. Additionally, in the past decade alone, a number of engrossing, provocative books have been published on various related issues ranging from vaccines against specific diseases to vaccine safety and policy. Yet there remains a significant gap in the literature – the history of vaccines.

Vaccines: A Biography seeks to fill a void in the extant literature by focusing on the history of vaccines and in so doing, recounts the social, cultural, and scientific history of vaccines; it places them within their natural, historical context. The book traces the lineage – the "biography" – of individual vaccines, originating with deeply rooted medical problems and evolving to an eventual conclusion. Nonetheless, these are not "biographies" in the traditional sense; they do not trace an individual's growth and development. Instead, they follow an idea as it is conceived and developed, through the contributions of many. These are epic stories of discovery, of risk-takers, of individuals advancing medical science, in the words of the famous physical scientist Isaac Newton, "by standing on the shoulders of giants." One grant reviewer described the book's concept as "triumphalist"; although meant as an indictment, this is only partially inaccurate. What in medicine could be more triumphant than conquering disease?

A prominent theme woven throughout the book is the interdependence of incremental scientific advances and investigators on one another and how these ultimately led to practical, preventive solutions to major public health problems in society. The book is nearly chronological in its approach to this history. Each chapter is written to stand independently, yet those who read it from cover to cover will discover that despite its broad scope, it is the "smallness" of the world of vaccine science and the inter-relatedness of its themes and characters that fascinates. The book is organized such that anchoring chapters are interspersed throughout; their purpose is to essentially introduce eras, reflecting the way in which I have chosen to present this biographical history. Smallpox represents a disease-specific chapter and an anchor chapter as well, because it served as the sentinel moment – the starting point – from which all vaccine science is measured. From there, vaccines developed in clusters proximate to major scientific developments. The evolution of microbiology and immunology as distinct sciences in the nineteenth century paved the way for the first productive period of vaccines in a manner analogous to what the discovery of viruses and subsequently tissue culture methods meant for the fruitful vaccine period of the latter half of the twentieth century. The book ends with its final anchor chapter, one meant to provide a foundation for what may be the next surge in vaccine science related to molecular and genomic medicine.

Why another book about vaccines now? There are, to be fair, two forces that have acted in synergistic fashion and driven me to write this book at this time. First, it is a subject about which I am passionate; it is, literally and figuratively, in my blood. I find the histories inspirational yet humbling, fascinating yet at times tragic. They have all the trappings of fiction: strong protagonists who succeed against sometimes great odds, interpersonal conflicts, deceit, political intrigue, ethical dilemmas, and dramatic, if not staged, events. They are set in the major centers of Europe and the United States, on farms and in slums, and in exotic venues from Calcutta to French Indochina to Cairo to Panama. They occur in the halls of academia, the chambers of government, and on the battlefields of war.

The other, compelling motive to pursue this project at this juncture is that many of the vaccine biographies detailed in this book describe events that occurred in the recent past; many of those intimately involved in these histories are still with us, some are still actively contributing to the field of vaccinology; many have contributed chapters to this work. Of course, many of the pioneers are gone, although in some cases quite recently. I see *Vaccines: A Biography* as an appropriate way in which to honor each of them and pay tribute to their efforts to improve the lot of humankind.

As with any such project of this scope and magnitude, success depends on the help of a dedicated staff and colleagues who are committed to excellence. The individual chapter authors have produced truly outstanding biographical histories – many of these individuals devoted much of their professional lives to their subjects and were major contributors to the vaccines of which they write, circumstances that are transparent upon reading their work. I am indebted to them for endeavoring to produce an accurate, thoroughly readable, historical record of these stories. Margo Katz coordinated the project, and Kathy Bollesen provided reliable and constant administrative assistance; both once again showed their mettle through their devotion to its successful completion. I am fortunate to work with such excellent people. Dr. David Greer, Dean Emeritus of Brown Medical School and a close personal friend, colleague, and mentor, carefully reviewed the manuscript and provided valuable insights that improved the work. I am grateful for his guiding presence. My wife Debbie, the love of my life, and my sons, Nick and Sam, provided a constant source of support and listened as these stories came to life. I hope that those who read this work learn as much and enjoy it as much as I did in writing and editing it.

Providence RI Andrew W. Artenstein

Contents

Contributors

Andrew W. Artenstein, MD, FACP, FIDSA
Department of Medicine, Memorial Hospital of Rhode Island,
111 Brewster Street, Pawtucket, RI 02860, USA
artenstein@brown.edu

Nicholas C. Artenstein, BA
Teach-for-America, 2601 N. Howard St.,
Baltimore, MD 21218, USA

Anne-Marie Balazuc, PhD
Institut Pasteur, 10 r Charcot, 92200 Neuilly sur Seine, Paris, France
abalazuc@pasteur.fr

Leonard N. Binn, PhD
Division of Viral Diseases, Walter Reed Army Institute of Research,
Silver Spring, MD 20910-7500, USA
leonard.binn@us.army.mil

Baruch S. Blumberg, MD
Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19111, USA
baruch.blumberg@fccc.edu

Hervé Bourhy
Institut Pasteur, UPRE Lyssavirus Dynamics and Host Adaptation, National Reference Centre for Rabies, WHO Collaborative Centre for Reference and Research on Rabies, 28 rue du docteur Roux, 75724 Paris Cedex 15, France
hbourhy@pasteur.fr

Charles C.J. Carpenter, MD
The Miriam Hospital, 164 Summit Avenue, Providence, RI 02906, USA
charles_carpenter@brown.edu

Jean-Marc Cavaillon, DrSc
Institut Pasteur, 28 Rue Doct Roux, 75015 Paris, France
jmcavail@pasteur.fr

Alan Cross, MD
University of Maryland School of Medicine, 655 West Baltimore Street, Room S9D12, Baltimore, MD 21201-1559, USA
across@medicine.umaryland.edu

Penelope H. Dennehy, MD
Rhode Island Hospital, 593 Eddy Street, POB 018, Providence, RI 02903, USA
pdennehy@lifespan.org

Ian H. Frazer, MD, MB ChB
Professor/Director, Diamantina Institute for Cancer Immunology and Metabolic Medicine, The University of Queensland, 4th Floor Research Extension, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, QLD 4102, Australia
i.frazer@uq.edu.au

Kathleen Gallagher, ScD
Centers for Disease Control and Prevention, 1600 Clifton Rd, Mail Stop A-47, Atlanta, GA 30333, USA
kgallagher1@cdc.gov

Anne A. Gershon, MD
Columbia University Medical Center, 630 W. 168th Street, 3rd Floor, Room 435, New York, NY 10032, USA
aag1@columbia.edu

Marina Gheorghiu, MD
Institut Pasteur, 10 r Charcot, 92200 Neuilly sur Seine, Paris, France

John D. Grabenstein, RPh, PhD
Medical Affairs and Policy, Merck Vaccines and Infectious Diseases, West Point, PA, USA
john_grabenstein@merck.com

Scott B. Halstead, MD
Director, PDVI Research & Development, 5824 Edson Lane, N., Bethesda, MD 20852, USA
halsteads@erols.com

Richrd B. Hornick, MD
Orlando Regional Healthcare, Internal Medicine Residency Program, 86 W Underwood Street, Suite 102, Orlando, FL 32806, USA
dickh@orhs.org

Samuel Katz, MD
Wilburt C. Davison Professor & Chairman Emeritus, Department of Pediatrics, Duke Children's Health Center, P.O. Box 2925, T915C, 2301 Erwin Road, Durham, NC 27710, USA
katz0004@mc.duke.edu

Micheline Lagranderie, PhD
Institut Pasteur, 10 r Charcot, 92200 Neuilly sur Seine, Paris, France
mlagrand@pasteur.fr

Stanley M. Lemon, MD
Department of Microbiology and Immunology, University of Texas Medical Branch, MRB, Route 0428, Galveston, TX 77555, USA
smlemon@utmb.edu

Adel Mahmoud, MD, PhD
Department of Molecular Biology, Woodrow Wilson School of Public and International Affairs, Lewis Thomas Laboratory, Princeton University, Room 228, Princeton, NJ 08544, USA
amahmoud@princeton.edu

Thomas P. Monath, MD
Kleiner Perkins Caufield & Byers, Pandemic & Biodefense Fund, 21 Finn Road, Harvard, MA 01451, USA
tmonath@kpcb.com

Steven M. Opal, MD
Department of Medicine, Memorial Hospital of Rhode Island, 111 Brewster Street, Pawtucket, RI 02860, USA
steven_opal@brown.edu

Walter Orenstein, MD
Integrated Health Solutions Development, Global Health Program, Bill & Melinda Gates Foundation, P.O. Box 23350, Seattle, WA 98102, USA
worenst@emory.edu, walter.orenstein@gatesfoundation.org

David Oshinsky, PhD
Department of History, College of Liberal Arts, The University of Texas at Austin, 1 University Station, B7000, Austin, TX 78712, USA
oshinsky@mail.utexas.edu

Annick Perrot
Curator, Institut Pasteur, 28 Rue Doct Roux, 75015 Paris, France
aperrot@pasteur.fr

Stanley A. Plotkin, MD
Vaxconsult LLC & Department of Pediatrics, University of Pennsylvania, PA, USA
stanley.plotkin@vaxconsult.com

Phil Russell, MD
Sabin Vaccine Institute, 11909 Coldstream Drive, Potomac, MD 20854, USA
pkrussell@aol.com

Peter C.B. Turnbull, PhD
c/o Dstl, Porton Down, Salisbury, Wiltshire SP4 0JQ, UK
peterturnbull@tesco.net

About the Editor

Andrew W. Artenstein, MD, is the Physician-in-Chief of the Department of Medicine and the Founding Director of the Center for Biodefense and Emerging Pathogens at Memorial Hospital of Rhode Island and Professor of Medicine and Community Health at the Warren Alpert Medical School of Brown University. An infectious diseases physician actively engaged in the arenas of research, teaching, clinical medicine, and public health, he is the author of numerous articles and book chapters on subjects related to infectious diseases, vaccines, and biodefense.

Author Biographies

Andrew W. Artenstein, MD
Physician-in-Chief, Department of Medicine and Founding Director of the Center for Biodefense and Emerging Pathogens, Memorial Hospital of Rhode Island; Professor of Medicine and Community Health, the Warren Alpert Medical School of Brown University. Dr. Artenstein has been involved in vaccine research throughout his career and has concurrently pursued his passion for medical history.

Nicholas C. Artenstein, BA
Currently a Teach-for-America Corps member in Baltimore, MD after graduating from Carleton College with a degree in economics.

Anne-Marie Balazuc, PhD
Researcher at the Institut Pasteur, Paris involved in the production and quality assurance of BCG and all pharmaceutical aspects in the medical development of vaccine candidates.

Leonard N. Binn, PhD
A virologist at the Walter Reed Army Institute of Research in Washington, DC for more than 50 years. During his long tenure there, Dr. Binn has participated in the development and evaluation of numerous human and animal viral vaccines and has described several new viruses.

Baruch S. Blumberg, MD
Senior Advisor to the President of Fox Chase Cancer Center and Professor of Medicine and Anthropology at the University of Pennsylvania. He has also served as Senior Advisor to the Administrator for Biology at the National Aeronautics and Space Administration (NASA) in Washington, DC and as the Director of the NASA Astrobiology Institute. Dr. Blumberg won the Nobel Prize in Medicine in 1976 for his discovery of the hepatitis B virus; he and his colleagues discovered the virus in 1967, developed the first diagnostic test shortly thereafter, and invented the first vaccine in 1969.

Hervé Bourhy, PhD
Head of the UPRE Lyssavirus Dynamics and Host Adaptation at the Institut Pasteur, Paris.

Charles C.J. Carpenter, MD
Director of the Lifespan/Tufts/Brown Center for AIDS Research and Professor of Medicine, The Warren Alpert Medical School of Brown University. Dr. Carpenter has devoted his highly decorated career to the study of infectious diseases and public health and has made numerous, significant contributions to international health. The early part of his career was focused on cholera research in Asia. He continues to serve in consulting and advising roles on numerous bodies involved in public health and health policy.

Jean-Marc Cavaillon, PhD
Director of the Department of Infection and Epidemiology, Head of the Cytokine and Inflammation Unit, and Professor at the Institut Pasteur in Paris. Dr. Cavaillon's research interests are centered on the immunology of sepsis, but he has had a career-long interest in the history of microbiology and the Institut Pasteur.

Alan S. Cross, MD
Professor of Medicine and Chief, Section of Vaccine Adjuvants and Innate Immunity, Center for Vaccine Development, University of Maryland School of Medicine. Dr. Cross has spent the majority of his career in both military and academic environments engaged in productive, translational research on vaccines against bacterial pathogens.

Penelope Dennehy, MD
Director, Division of Pediatric Infectious Diseases, Rhode Island Hospital, and Professor and Vice Chair for Academic Affairs, Department of Pediatrics, Warren Alpert Medical School of Brown University. Dr. Dennehy has been a key contributor to the strategic development and study of vaccines against pediatric viral pathogens; her most recent efforts have focused on rotavirus vaccines.

Ian H. Frazer, MD, MB ChB
Director of the Diamantina Institute of Cancer Immunology and Metabolic Medicine of the University of Queensland at the Princess Alexandra Hospital in Brisbane, Australia; Professor of Medicine, University of Queensland. Dr. Frazer's career in medical research has been devoted to the study of vaccines to prevent human papillomavirus infection and its associated cancers. His group developed the technology that formed the basis for recently commercialized vaccines.

Anne A. Gershon, MD
Director of the Division of Pediatric Infectious Diseases and Professor of Pediatrics at Columbia University College of Physicians and Surgeons. Dr. Gershon has spent a large portion of her career studying the varicella-zoster virus; her research on the safety and efficacy of the varicella vaccine in leukemic children was crucial to its licensure.

Marina Gheorghiu, MD
Formerly, BCG Department Chief at the Institut Pasteur in Paris. Dr. Gheorghiu devoted her entire career to the study of the immunology of tuberculosis and BCG vaccines. She has served as a consultant to the World Health Organization and other

international bodies on the development and use of BCG vaccine and is widely considered to be one of the foremost global authorities on this vaccine.

John D. Grabenstein, RPh, PhD
Senior Director for Adult Medical Affairs at Merck Vaccines and Infectious Diseases, providing scientific guidance and leadership for Merck's international vaccine enterprise. Prior to this, he served more than 25 years in the US Army, directing the Military Vaccine Agency and serving as scientific director of the Department of Defense immunization programs affecting more than 9 million individuals worldwide.

Kathleen Gallagher, DSc, MPH
Team Leader for measles, mumps, rubella, and polio activities within the Epidemiology Branch, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, US Centers for Disease Control and Prevention (CDC). In that capacity, she oversees all activities related to surveillance and investigation of domestic cases of these infections. Dr. Gallagher has spent most of her career involved in the epidemiology of communicable diseases.

Scott B. Halstead, MD
Research Director, Pediatric Dengue Vaccine Initiative, International Vaccine Institute, Seoul, Korea. Dr. Halstead has devoted the vast majority of his illustrious career to problems in international health, tropical infectious diseases, and the development of vaccines against viral pathogens of these environments. He has made major contributions to the pathophysiology and immunology of dengue and to vaccines against Japanese encephalitis virus.

Richard B. Hornick, MD
Department of Medicine, Orlando Health, formerly Chairman, Department of Medicine at the University of Rochester. Dr. Hornick spent a large portion of his career in vaccine research directed against a variety of infectious diseases, including typhoid fever and cholera.

Samuel L. Katz, MD
Wilburt Cornell Davison Professor and Chairman Emeritus of Pediatrics at Duke University. Dr. Katz performed his research fellowship in virology and infectious diseases in the Enders laboratory at Harvard and with John Enders, is credited with developing the attenuated measles vaccines now used worldwide. His career focused principally on vaccine research, development, clinical studies, and policy. Dr. Katz is a recipient of the Gold Medal of the Sabin Vaccine Institute and has chaired numerous national and international panels and advisory groups dealing with vaccines and their use.

Micheline LaGranderie, PhD
Research scientist in the Immunotherapy Laboratory, Institut Pasteur, Paris. Dr. LaGranderie has spent her career studying BCG vaccine and its associated host responses.

Stanley M. Lemon, MD
Director, Institute for Human Infections and Immunity, The University of Texas Medical Branch at Galveston, TX. He is the former Chair of the Advisory Committee on Vaccines and Related Biologics of the US FDA and an internationally recognized authority on viral hepatitides. He was intimately involved in the research that led to effective, inactivated hepatitis A vaccines.

Adel Mahmoud, MD, PhD
Professor, Department of Molecular Biology, the Woodrow Wilson School of Public and International Affairs, Princeton University, Princeton, NJ; Adjunct Professor of Medicine, Case Western Reserve University and University Hospitals of Cleveland. Dr. Mahmoud has devoted his illustrious career in academic medicine and industry to vaccine research and has concomitantly served in a leadership role on numerous scientific advisory bodies and as a consultant to international governments and private foundations advocating for the development and use of vaccines to address health concerns in developing areas of the world.

Thomas P. Monath, MD
Partner, Pandemic and Biodefense Fund, Kleiner Perkins Caufield and Byers and Adjunct Professor, Harvard School of Public Health. Dr. Monath has devoted his career to vaccine research through 24 years in the US uniformed services and a continuation of his work in industry, where he has directed research and development on vaccines against dengue, West Nile, Japanese encephalitis, Clostridium difficile, and successful new generation vaccines against smallpox and yellow fever.

Steven M. Opal, MD
Chief, Division of Infectious Diseases, Memorial Hospital of Rhode Island and Professor of Medicine, The Warren Alpert Medical School of Brown University. Dr. Opal has devoted his career to the study of bacterial pathogenesis, the immunology of sepsis, and the prevention of infectious diseases. He has a deep and abiding interest in the history of microbiology.

Walter A. Orenstein, MD
Deputy Director for Vaccine-Preventable Diseases in Integrated Health Solutions Development of the Global Health Program at the Bill and Melinda Gates Foundation. Previously, Dr. Orenstein served as Director of the Emory Vaccine Center and the Program on Vaccine Policy and Development there. He also served as Director of the National Immunization Program at the CDC, where he developed, promoted, and expanded new vaccination strategies to enhance disease prevention. Dr. Orenstein has spent his career in the arenas of vaccine science and policy and co-authored the leading textbook in the field of vaccinology.

David M. Oshinsky, PhD
Professor and Jack S. Blanton Chair in History, University of Texas, Austin, TX and Distinguished Scholar in Residence at New York University. Dr. Oshinsky is a leading historian of modern American politics and society and has written a number of prize-winning books. He was awarded the Pulitzer Prize in History for his most

recent work “Polio: An American Story” that examines the medical and social history of the disease and is the subject of a recent documentary.

Annick Perrot, PhD
Curator of the Institut Pasteur Museum, Paris.

Stanley A. Plotkin, MD
Emeritus Professor of the University of Pennsylvania, Adjunct Professor of the Johns Hopkins University, and Executive Advisor to Sanofi Pasteur. He previously served as a Professor of Virology at the Wistar Institute and Senior Physician at the Children’s Hospital of Philadelphia, and was Medical and Scientific Director at the vaccine manufacturer Pasteur-Mérieux-Connaught in France. In his illustrious career, Dr. Plotkin has received numerous international awards and honors, has chaired numerous professional and governmental commissions involving vaccines and infectious diseases, and has written extensively on these issues. He is the editor of the standard textbook on vaccines. Dr. Plotkin developed the rubella vaccine now in worldwide use and is the co-developer of the newly licensed pentavalent rotavirus vaccine. He has worked extensively on the development and application of other vaccines including anthrax, oral polio, rabies, varicella, and cytomegalovirus.

Phillip K. Russell, MD
Major General (ret), US Army; Professor Emeritus, Johns Hopkins School of Hygiene and Public Health. His career, both in military and in civilian environments, has been dedicated to the successful development and deployment of several vaccines. He continues to serve in an advising role on numerous boards and foundations related to international vaccines.

Peter C.B. Turnbull, PhD
Dr. Turnbull spent the majority of his career devoted to anthrax research in the UK Department of Health’s Public Health Laboratory Service. He also spent portions of his career at the South African Institute for Medical Research and following his retirement from UK Government service, he worked in the Biological Defense Research Directorate at the Naval Medical Research Center in Maryland and the Centers for Disease Control and Prevention in Atlanta. Dr. Turnbull provides expert advice on anthrax to the World Health Organization.

Chapter 1
Vaccinology in Context: The Historical Burden of Infectious Diseases

Andrew W. Artenstein

> *As a rule, the scientist takes off from the manifold observations of his predecessors….The one who places the last stone and steps across to the terra firma of accomplished discovery gets all the credit…*
>
> John Enders

In a 1977 article summarizing 40 years of his involvement in vaccine research, Jonas Salk, the renowned and controversial force behind the first effective polio vaccine, coined the term "vaccinology" to comprehensively describe his chosen field (Salk and Salk 1977). The term is meant to encompass the broad areas of discipline requisite for the science of vaccines: microbiology, epidemiology, pathogenesis, and immunology. In defining this novel branch of science, Salk recognized that vaccinology formed a nexus between medicine, public health, sociology, and biochemistry. He understood the rich history of scientific accomplishments that defined the field and formed an inextricable link with the past.

Arguably, the concept and practice of vaccination against infectious diseases has resulted in greater benefits to human health than any other cultural, social, or scientific advance in the history of humanity. As a testament to their historical importance, vaccines were ranked first among the ten greatest public health achievements of the twentieth century (Centers for Disease Control and Prevention 1999). Through their use, scourges of nature have been eradicated, controlled, or rendered irrelevant, and generations of children have survived into adulthood, unscathed by diseases that would have been lethal earlier in history. Vaccines harnessed the human immune system to its fullest extent long before the fundamental tenets of immunology were described; the concepts that form the basis of vaccine science have since been extended to a plethora of infectious and noninfectious diseases.

A.W. Artenstein (✉)
Department of Medicine, Center for Biodefense and Emerging Pathogens,
Memorial Hospital of Rhode Island, The Warren Alpert Medical School of Brown University,
Providence, RI, USA
e-mail: artenstein@brown.edu

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The formal history of vaccination, from a scientific standpoint, traditionally dates from Edward Jenner's landmark experiments with cowpox in 1796, although it would be nearly a century before the practice received its name, an honor bestowed posthumously upon Jenner by its most celebrated scientific proponent, Louis Pasteur (Moulin 1996). Jenner inoculated a neighbor's boy with purulent material from a milkmaid's hand lesion in Berkeley, England (Moloo and Artenstein 2008). The boy, 8-year-old James Phipps, was subsequently shown to be protected against a smallpox challenge. Jenner followed this initial experiment with a systematic study of the protective effect of cowpox on variola. The related concept that humans could be protected against disease by intentionally exposing them to the supposed cause of the malady probably arose many centuries before Jenner, although this remains poorly documented.

According to legend, Mithridates VI, King of Pontus on the Black Sea in Asia Minor from 120 to 63 BC, ingested daily, sublethal doses of poison in order to build his tolerance to such agents (Parish 1965). Although this behavior was presumably motivated by suspicion bordering on paranoia of his impending assassination, it may have been warranted; his mother killed his brothers and may have assassinated their father, King Mithridates V, in her attempt to usurp the throne (Marsh and Scullard 1953). It did not help matters that he was also a formidable enemy and thus a target of the Roman Empire. But the strategy may have worked; when he was eventually defeated by Pompey and "wished to die by poison, he was unable," most likely due to acquired resistance (Justinus 1853). Mithridates' concoction of plant oils and resins became the basis for the universal antidotes Mithridatium and Theriac (Griffin 2004; Norton 2006).

Various other forms of vaccination were practiced throughout pre-Jennerian history. Buddhists in India in the seventh century supposedly ingested snake venom to protect themselves from its fatal effects (Plotkin and Plotkin 2008). At least four methods of variolation were probably in use in China in the sixteenth century: placing cotton instilled with either pus or scabs from lesions in the nostrils of healthy children; blowing powdered scabs into the nostrils using a thin silver tube; and dressing healthy children in clothing worn by smallpox-infected individuals (Leung 1996). In the midst of a measles epidemic in Edinburgh in 1758, Scottish physician Francis Home attempted to inoculate healthy individuals with skin lesion material from infected individuals. Using a mixture of blood and affected skin, he inoculated a small group of children, resulting in clinically attenuated illness and protection against wild type measles (Enders 1964).

These early forays into vaccination were based on empiricism and practical realities. Jenner and his immediate predecessors also appear to have based their theories on empiric observations from nature. The common denominator was that their observations were supported by a substantial experiential tradition. Such "rational empiricism" (Hilleman 2000) was likely born from generations of struggles against epidemic and endemic infectious diseases.

Epidemic infectious diseases in ancient cultures were believed to be of divine etiology (Conrad et al. 1995; Brier 2004). Many had a profound effect upon civilizations. Ancient Greek hegemony never recovered from the devastation wrought by the plague of Athens that began in 430 BC, early in the Peloponnesian War, and was caused by measles or perhaps another highly transmissible infectious disease (Cunha 2004). The Antonine plague of 165–169 AD, probably due to smallpox, originated in the eastern reaches of the Roman Empire (modern-day Iraq) before it became a pandemic; it played a significant role in the inexorable decline of that superpower (Fears 2004).

Recurring pandemics and sporadic, catastrophic, focal outbreaks of endemic infectious diseases have played important roles in shaping the course of human history (Zinsser 1934; Diamond 1997; Cantor 2002; Trevisanato 2004). The Justinian plague of 541–544 AD was just the opening salvo in 11 bubonic and pneumonic plague epidemics that disseminated and resurged in cycles throughout the known world of that time over a period of 200 years (Conrad et al. 1995; Asad and Artenstein 2009). It has been estimated that up to 50% of the population perished, contributing to major sociopolitical changes in the Byzantine Empire and leading Europe into the Middle Ages (Drancourt and Raoult 2002).

Plague, in the form of "The Black Death," arrived again in Sicily in 1347 via the trade routes from Asia, devastating the population of Europe and likely changing the course of history through its impact on geopolitics, the balance of military power, medieval economics, and almost all aspects of daily and cultural life (Diamond 1997; Cantor 2002). The impact of the epidemic in Europe may have extended to the human genome, altering the genetic predisposition to future infectious diseases in that population via selective mutational pressures (Galvani and Slatkin 2003).

The intimate, complex relationship between human beings and communicable diseases was a consequence of human social evolution. Early humans operated as small bands of hunter-gatherers; their relatively short life spans were the result of food shortages rather than epidemic infectious diseases (Diamond 1997). Diseases that relied on person-to-person transmission for persistence or amplification would have either been extremely limited in their infectious range by small group size or would have been extinguished along with their hosts. With the advent of food-producing, large, dense, immobile, agricultural societies, conditions were such that epidemics of infectious diseases could be maintained (Diamond 1997). Social urbanization magnified their epidemic potential by facilitating transmission. Thus it is not surprising that infectious diseases such as smallpox, plague, tuberculosis, dysentery, and pneumonia were primarily responsible for the limited life expectancy and death of a significant proportion of the population in early modern Europe (Conrad et al. 1995).

Because communicable diseases were so prevalent, European societies became immunologically experienced in terms of their exposures to many pathogens. Hence, over time many infectious diseases persisted as endemic, sporadic threats that became part of the morbid landscape but with less explosive mortality (Conrad et al. 1995). In contrast, the effect of communicable diseases on immunologically naïve populations was potentially cataclysmic (McNeill 1976). Examples of this phenomenon abound in medical and historical literature. Columbus' first voyage across the Atlantic in 1492 unleashed Europe's repertoire of epidemic infectious diseases on the virgin population of the New World, a dynamic that continued with successive Old World incursions into the Americas over the next 150 years.

Indigenous populations were decimated; smallpox epidemics ravaged the island of Hispaniola in the first quarter of the sixteenth century, reducing the population by more than 95% (Cook 1998).

Other Native American societies of the Caribbean basin and later Mexico, Guatemala, and Brazil fell victim to additional infections: dysentery, influenza, vivax malaria, and measles among them. With epidemic smallpox, introduced by Spanish forces, rampaging through the Indian population of central Mexico, Hernán Cortés was able to easily subjugate the Aztec Empire with fewer than 500 men in 1521(Hopkins 1983; Cook 1998). His compatriot, Francisco Pizarro, was the beneficiary of a similar result against the Incas in Peru a decade later (Hopkins 1983).

An analogous fate was met by other virginal populations when novel diseases were introduced via friendly or hostile visitors from endemic areas. Yellow fever virus entered the New World through the transatlantic slave trade from Africa (Artenstein et al. 2005); it caused recurrent, highly lethal epidemics in coastal areas of the Americas from the seventeenth century to the early part of the twentieth century. In Philadelphia in 1793, the disease killed approximately 10% of the city's population (Murphy 2003); its decimation of Napoleon's expeditionary forces in Haiti in 1802 convinced the General to abandon his imperial plans for the Americas and to sell the Louisiana Territory to the United States (Artenstein et al. 2005). Yellow fever again made its mark on history in the early twentieth century as it forced the French out of the Panama Canal development process and nearly derailed the American effort there (McCullough 1977). Measles was imported to the isolated, North Atlantic Faroe Islands in 1846 by an infected carpenter and within 6 months, nearly 80% of the population of less than 8,000 had become infected (Panum 1847).

The observations of Jenner and his predecessors were informed by the historical burden of infectious diseases as viewed through the lens of "rational empiricism." Their vaccinology descendants, beginning with Louis Pasteur in the nineteenth century, contributed to and benefited from major developments in medicine and science (Bynum 1994). Their innovations advanced vaccine research into a distinct science that produced, in numerous instances throughout its history, spectacular results (Chase 1982; Allen 2007).

The history of vaccinology (Fig. 1.1) parallels the history of human scientific endeavor and illustrates an important precept common to all scientific inquiry: major advances generally stem from incremental progress that itself derives from the accumulation of ordered, experimental observations synthesized from a variety of fields. Scientific advances are often non-linear, resulting from shifts in existing paradigms; landmark discoveries generally do not occur in a vacuum but are instead based on expansions of pre-existing scientific thought, sometimes with tumultuous consequences (Kuhn 1996). Additionally, advances in technology inherently drive advances in science, and both are frequently products of specific unmet needs. The history of vaccinology represents the individual and collective stories of inquisitive minds, thought leaders, risk-takers and those that stood "on the shoulders of giants" to improve the health of humanity.

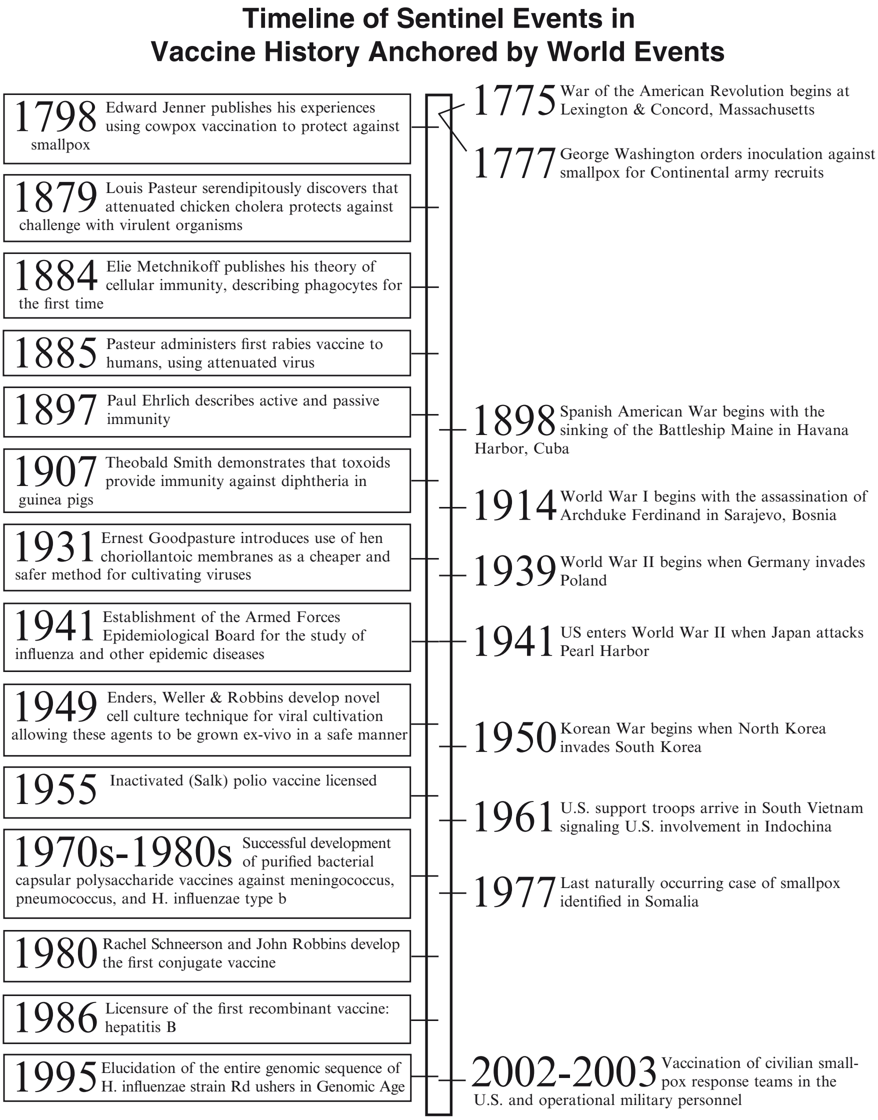

Fig. 1.1 Vaccine development within the historical context of world events since Jenner (Military Medicine: International Journal of AMSUS, Vol.170, April Supplemental, pp 3-11, reproduced with permission)

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Chapter 2
Smallpox

Andrew W. Artenstein

Smallpox represents an appropriate embarkation point for a historical examination of vaccines because this disease was the first against which a scientifically studied vaccine was successfully implemented in humans. During the nearly 90 years between Jenner's systematic experiments with cowpox and Pasteur's clinical use of rabies vaccines, the next to be used in humans, advances in vaccine science derived largely from the expansion of knowledge regarding smallpox vaccination and its beneficial and harmful effects. As experience with smallpox vaccines evolved through the nineteenth and first half of the twentieth centuries, it became evident that the regional successes of vaccination could be generalized to all areas of the world; thus, the global campaign to eradicate smallpox was born. Although its ultimate success established triumphant historical precedent, smallpox vaccines remain an active issue three decades after smallpox was eradicated as a natural cause of human disease.

2.1 A Brief History of Smallpox

In many ways, it stands to reason that vaccination against smallpox, or variola, would be the benchmark by which future vaccines would be assessed. Historically, smallpox occupies a position as the greatest disease scourge of humankind; its impact on civilizations has been amply documented in a variety of media including written texts, works of literature, and objects of art. Although it is problematic from historical records to accurately classify diagnoses of smallpox before approximately 1,000 AD, descriptions of a clinically compatible illness appeared in ancient writings from Asia during the first millennium AD (Fenner et al. 1988). Characteristic

A.W. Artenstein (✉)
Department of Medicine, Center for Biodefense and Emerging Pathogens,
Memorial Hospital of Rhode Island, The Warren Alpert Medical School of Brown University,
Providence, RI, USA
e-mail: artenstein@brown.edu

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findings of the disease were noted in the mummified human remains of three Egyptians dating from more than 1,000 years before the birth of Christ (Ruffer and Ferguson 1911; Hopkins 2002), but the conspicuous absence of descriptions consistent with smallpox from Egyptian medical writings of the period raises questions regarding its occurrence.

Ancient medical scholars such as Ko Hung in China, Vagbhata in India, and al-Razi in Baghdad described the epidemiology and clinical appearance of smallpox in the fourth, seventh, and tenth centuries AD, respectively (Fenner et al. 1988). Epidemic disease, likely originating in Asia, entered naïve populations through invading armies and foreign traders via routes through North Africa and the Mediterranean basin (Fenner et al. 1988). Highly lethal, documented outbreaks recurred throughout the world during the latter half of the second millennium, accounting for tens of millions of deaths from this disease. Smallpox became endemic on the Indian subcontinent, throughout Asia, Africa, and Europe in this period and was imported into the New World by Old World explorers, conquerors, colonizers, and slave traders.

The scope of devastation wrought by the disease altered the course of human history. It may have been a factor in the decline of the Roman Empire (Fears 2004); smallpox was perhaps the most important of an array of transmissible diseases that resulted in the decimation of indigenous tribes of the Americas during the sixteenth century (Cook 1998; Hopkins 2002); and it altered the geopolitical landscape of the preindustrial world by deposing monarchs and halting armies. During the latter part of the eighteenth century, smallpox accounted for 10% of the mortality in some of Europe's major cities; most of this occurred in children (Hopkins 2002). Epidemics, with their attendant morbidity and mortality, continued to occur throughout the developed world until they were checked by the introduction of widespread vaccination.

2.2 Pre-Jennerian Smallpox Vaccine History

The concept of using inoculations of pus or scabs from smallpox-infected individuals to mitigate the severity of natural variola, the process of "variolation," probably derived from empiric observations that smallpox survivors were protected against re-infection. Variolation generally produced a localized, less severe form of disease than naturally acquired smallpox. Although it was associated with dissemination and mortality in a small percentage of individuals, approximately tenfold lower than that following naturally acquired smallpox, variolation could lead to transmission of smallpox by contact. The procedure may have been practiced in Egypt in the thirteenth century and was known to be used in India in the sixteenth and parts of Africa and China in the late seventeenth centuries (Fenner et al. 1988).

Although various forms of variolation may have been sporadically employed in China as early as the eighth century, it is difficult to identify substantiating documentation of its practice there until the seventeenth century (Buck 2003). Inoculation, another name for the procedure, is described in a medical text from 1695. A more detailed account, *The Golden Mirror of the Medical Tradition*, published in 1742 and apparently endorsed by the Chinese Imperial court, may have enabled variolation to become part of the mainstream medicine of the time and to be disseminated throughout eighteenth century Chinese society (Leung 1996). This text describes four distinct methods of variolation: placing pus from smallpox lesions or scabs into the nares of healthy children; dressing healthy children in clothing worn by infected individuals; and nasal insufflation of dried, powdered, smallpox crusts derived from patients in the late phases of disease via a silver tube (Leung 1996). The latter method may have been preferred, in part because of the belief that the respiratory tree provided the pathway through which the effects of variolation could circulate to the other, traditional, visceral zones of Chinese medicine (Leung 1996).

Documentation of variolation in India began in the sixteenth century; the practice gradually spread from there through parts of southwest Asia, central Europe via the Balkans, and Africa with Arab slave traders (Fenner et al. 1988). Official Russian emissaries may have learned the method from Chinese authorities and exported variolation to Eastern Europe (Buck 2003). The technique may have been introduced into the Ottoman Empire in the seventeenth century by Seljuk, ancestral Turks with connections to southwest Asia, or by Circassian traders from the Caucasus and the regions around the Black Sea, whose women were highly prized by the Turkish Sultan. These women, who were sold to the Sultan's harem, were apparently protected as children against the disfigurement of smallpox by inoculation in inconspicuous areas of their bodies (Dinc and Ulman 2007).

Turkey, ruled by the Ottomans for more than 600 years beginning in the fourteenth century, represented a geographic bridge between East and West. Its culture was mosaic, a melting pot blending parts of both societies and hosting a variety of European visitors who witnessed innovative practices introduced from exotic places throughout Asia and Africa. Variolation was one such practice. Sporadic reports of its use may have circulated via such travelers to the Far East or Africa, as references to the procedure appeared in correspondences prior to the turn of the eighteenth century (Stearns and Pasti 1950). But it became a subject of active discourse among scientific circles in the early part of the eighteenth century in Great Britain; the Royal Society of London first heard presentations describing the Chinese technique of intranasal variolation in 1700. In 1714 and 1716, independent reports by the physicians Timoni and Pylarini respectively, describing the Turkish method using the cutaneous route were read there (Woodward 1714; Huth 2006). These reports engendered mild scientific interest but did not result in acceptance of variolation or trials of the method by the conservative British medical establishment, who thought the procedure too risky and of dubious benefit (Miller 1957). This would begin to change a mere 5 years later due in part to the passion of an enlightened and politically connected layperson.

Lady Mary Wortley Montagu (1689–1762), the wife of the British ambassador to the Ottoman court, lived in Adrianople and Constantinople during the years 1717 and 1718. She was a keen observer of Turkish mores and society, attentively documenting these observations in her correspondence, poetry, and travel writings (Wortley Montagu 2000). She possessed an open mind and was favorably impressed with the practice of variolation, having experienced the death of her brother due to smallpox and suffered herself with this disease as an adult in 1715 – leaving her somewhat disfigured and without eyelashes (Wortley Montagu 2000). While in Adrianople she wrote to a friend in England of the technique of "engrafting" in which old women scratch a small amount of material from "a nutshell full of the matter of the best sort of smallpox" using a needle into multiple veins, usually on the extremities, of children or young adults (Wortley Montagu 2000). Shortly thereafter inoculated individuals developed fevers, a brief systemic illness, and subsequently recovered. Lady Montagu (Fig. 2.1) was sufficiently impressed that she had her 5-year old son inoculated by her personal, Scottish physician while in Turkey in 1718 and after her return to England, had her daughter undergo public variolation during a smallpox epidemic, an action that piqued royal interest in the procedure in part due to the social prominence of Lady Montagu (Stone and Stone 2002).

A series of further "experiments" followed the little girl's inoculation. With royal patronage and royal physicians directing the endeavor, experimentation with variolation was conducted on six condemned prisoners from London's infamous Newgate prison (Miller 1957). They were offered a sparing of the death penalty if they survived the ordeal; all demonstrated protection against a smallpox challenge (Parish 1965). After a small group of orphaned children was successfully variolated

Fig. 2.1 Lady Mary Wortley Montagu (Wellcome Library)

(Sloane 1756), the two daughters of the Princess of Wales were inoculated in 1722 and recovered uneventfully (Stone and Stone 2002).

The practice gradually grew in scope over the decade but was largely restricted to the upper classes in England and was still viewed by the medical profession as a somewhat risky procedure, associated with a 2% mortality rate, occasional severe morbidity, and the persistent threat of contact transmission to others, and one of unproven benefit (Stearns and Pasti 1950; Stone and Stone 2002). There was also considerable opposition from religious leaders. Nonetheless, an early, imperfect attempt to use medical statistics to justify smallpox inoculation during the latter part of the 1720s demonstrated a difference in mortality of nearly 90% comparing that of natural smallpox (approximately 17%) to that of variolation (approximately 2%) (Huth 2006).

At nearly the same time that Lady Montagu publicly introduced variolation into Great Britain, the procedure was employed in the New World in an attempt to quell the spread of epidemic smallpox. These events also reverberated in England and helped to facilitate the widespread acceptance of variolation there. In 1721, Zabdiel Boylston, a Massachusetts physician known as the first American-born physician to perform a surgical operation, the removal of a urinary stone, inoculated approximately 240 individuals in Boston with material from smallpox lesions (Harvard University Library Open Collection Program 2008). He had been introduced to the method by the Reverend Cotton Mather (1673–1726), a Harvard-educated cleric with a penchant and aptitude for medical science, who in turn had probably learned of the procedure in 1706 through one of his slaves, Onesimus, who claimed to have been inoculated in Africa (Brown 1988).

Mather (Fig. 2.2) was a controversial figure prior to his advocacy of variolation. His religious writings had served to further inflame the hysteria surrounding the Salem witchcraft trials of 1692; his views on medicine were tempered by a belief in the supernatural, apparent in his medico-religious treatise, *The Angel of Bethesda*, written but not published during his lifetime (Mather 1972). Mather's contributions in the arena of natural science had previously earned him election as a Fellow of the Royal Society of London and as such, he had read the reports of Timoni and Pylarini on inoculation and had become an advocate of the procedure (Silverman 1985). Advocacy turned to action during a smallpox epidemic in Boston in 1721 that affected half of the city's population, killing nearly 15% of its victims (Fenn 2001).

Mather appealed to Boston's medical establishment to use variolation to halt the epidemic; only Boylston heeded the call. Their actions with inoculation touched off a heated controversy in the city with both men experiencing significant public reprisals, including physical threats, from numerous quarters (Breen 1991). Nonetheless, mortality among the relatively small group of inoculated individuals, less than 3%, was significantly lower than that associated with natural smallpox infection (Stearns and Pasti 1950; Huth 2006). The New England experience, after its communication via the Royal Society to Britain, facilitated acceptance of the process with technical variations, spurred by ongoing smallpox epidemics in Great Britain during the first half of the eighteenth century and in other parts of Europe as the century progressed (Miller 1957; Fenner et al. 1988).

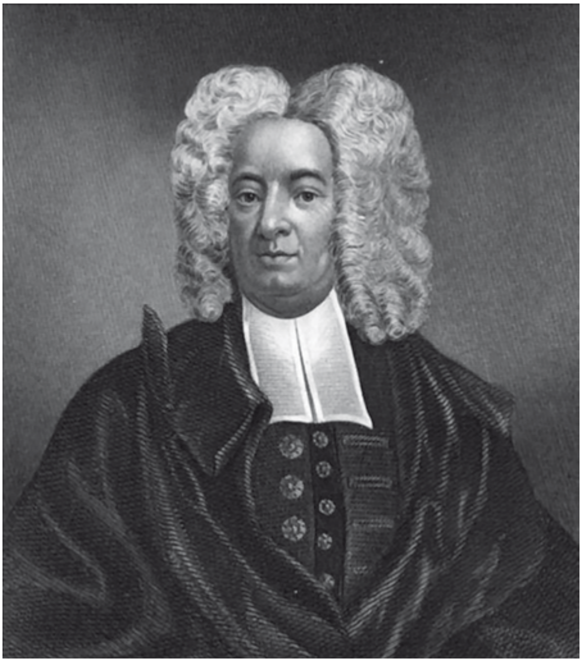

Fig. 2.2 Cotton Mather (American Antiquarian Society)

Variolation continued to be employed sporadically in Colonial America during the middle of the eighteenth century, largely as a response to epidemic disease. The American thought leader Benjamin Franklin was an important advocate; he reported favorable mortality data from its use during a smallpox outbreak in the early 1750s (Franklin 1759; Huth 2006). But inoculation was not only associated with significant disadvantages, including its cost, the prolonged preparatory and recovery periods, its attendant mortality rate, and its clear transmission risk to the unexposed, it was also still objectionable on religious, ethical, or medical grounds to a substantial segment of the population; the procedure was restricted by statute in every colony except for Pennsylvania (Hopkins 2002).

Inoculation became a strategic issue during the War of the American Revolution. British troops were, in large part, immunologically experienced with smallpox, a significant advantage over the colonists. General George Washington, commander of the Continental Army, had experienced smallpox first-hand as a teenager and appears to have been appropriately concerned with its potential impact on his susceptible troops from the earliest phases of the conflict. He instituted isolation measures where possible and used immune troops in selected situations as feasible. However, dwindling troop resources due to smallpox during the campaign in Canada over the winter of 1775–1776 and attrition due to the completion of enlistment terms in late 1776 led Washington to consider extreme measures to preserve his fighting force.