

Measles: Progress and Failure

John Hedley-Whyte, M.D., F.A.C.P., F.R.C.A. Debra R. Milamed, M.S.

Accepted: 15th December 2020

Provenance: Externally peer reviewed

Key Words: Gamma-globulins, Herd immunity, Measles, Vaccines, World War II

INTRODUCTION

“Every boy should know about Herd Immunity”, replied Professor Rutherford Morison to me¹ at the Annual (1938) Dipping of Cheviot sheep. My question to Professor Rutherford Morison had been suggested by my maternal grandfather who was a farmer and landowner of fields near Newcastle-upon-Tyne, where my father had been an Assistant Surgeon to Professor Rutherford Morison. As surgeons they both knew that I should be away from our home where my mother was being treated for post-partum thrombosis. Aged almost 5, I was staying with another famous surgeon, George A. Mason, later CBE, and his family nearby on Cheviot’s north side.

MUSGRAVE ENCOUNTERS

My first meeting with Director Ted Badger was in Hut 1, Musgrave Park^{1,2,3,4}. He asked me if I had had measles. I replied, “Yes, I had been treated in the dark to protect my conjunctivae”. “Good,” Badger replied. That was what ophthalmologist Rycroft—my brother’s godfather—had told him^{5,6}. I asked Badger if he had missed the Faroes in his small yacht sail from Yale⁷. “Yes,” he said. “We are going to use measles in our counter-attack against your father’s accusers, who are trying to have him court-martialed for attempting to obtain foods rich in vitamin A”^{5,8}. I, said Badger, am only a stand-in for Charles A. Janeway (CAJ) (Fig. 1), who was told to stay in Boston at Harvard to continue research with John F. Enders^{9,10} on the immunological control of mumps and measles in addition to his own work on plasma fractionation of blood^{11,12,13}. This had been ordered by CAJ’s neighbor, U.S. Secretary of War Henry L. Stimson (Fig 2). Badger informed me that “The Stimsons own thousands of acres next to the Janeways’ estate in the Adirondacks. The Stimsons also have a Long Island estate with its own polo field and Highland games”^{14,15,16}.

Badger also told me that CAJ’s father, Theodore Caldwell Janeway (1872-1917), a graduate of Yale and the College of Physicians and Surgeons of New York, was recruited in 1914 to be the first full-time Professor of Medicine at Johns Hopkins School of Medicine. He resigned this post in 1917 to enter the U.S. Army Medical Services as Major, and was assigned to the Office of the Surgeon General. CAJ’s father

died of pneumonia on December 17, 1917, when his son, CAJ, was my age.

Theodore Janeway’s father, Edward Gamaliel Janeway (1841-1911), a graduate of Rutgers with a Medical Degree from the College of Physicians and Surgeons of New York, had answered a call to Buffalo, NY six days after President William McKinley had suffered an assassin’s abdominal wound. Edward Gamaliel Janeway arrived too late to prevent the President’s death^{11,17}.

Edward Gamaliel Janeway was also a contemporary and neighbor of then Secretary of War Henry L. Stimson’s father, Lewis Atterbury Stimson (1844-1917). The latter graduated from Yale in 1863 and proceeded to study medicine at Bellevue Medical College in New York City. Lewis Atterbury Stimson had been the first in the U.S. to demonstrate and practice Lister’s method of antiseptic surgery, and in 1883 performed surgery on former president Ulysses S. Grant^{14,15}.

TED BADGER AND THE EPIDEMIOLOGY OF INFECTIOUS DISEASE

As fellow Yalies and Harvard Faculty, Badger and Enders were well acquainted with each other’s work. John F. Enders and his group had started their measles research in 1939 at the Enders’ estate on Long Island Sound at the time when Badger’s group were assessing the long-term health, including measles, of student nurses within the Harvard Medical School and its hospitals^{18,19}.

Badger later told me, while visiting our Windy Edge, Dunmurry home, that he had spoken to Rycroft further about the importance of vitamin A and health and nutrition for both the prevention of night-blindness and the amelioration of measles^{5,8,20,21,22}. CAJ was also passing this information on promptly to his Adirondacks neighbor, Henry L. Stimson. Did my father know that Stimson’s father had spread Lister’s anti-surgical antiseptics heritage in New York? CAJ’s father had been Head of Medicine at Hopkins after Osler and his grandfather, Edward Gamaliel Janeway had galloped to Buffalo from their Adirondack estate to try to save President McKinley.

A late post-mortem showed, “The mortally wounded

David S. Sheridan Professorship in Anaesthesia and Respiratory Therapy
Harvard University, 1400 VFW Parkway, Boston, MA 02132-4927 USA
Correspondence to: Prof. John Hedley-Whyte
Email: john_hedley-whyte@hms.harvard.edu

1 This and other first-person references are to the first author.



president's Rutherford Morison pouch had not been adequately explored"¹⁷. I knew that my father had worked for Professor Rutherford Morison at the Royal Victoria Infirmary in Newcastle-upon-Tyne and I told Badger that,"In 1938 Professor Rutherford Morison and I had supervised the dipping of Cheviot sheep." Professor Morison had wanted his invention BIPP, a preparation of iodoform, bismuth subnitrate and liquid paraffin developed for treatment of war wounds during World War I added to the sheep dip²³. This addition was declined, but used for treatment of wounded sheep.

JANEWAY'S STATESIDE CONTRIBUTION

YEAR	REPORTED CASES OF MEASLES IN THE BRITISH ARMED FORCES DURING WORLD WAR II ²⁹			REPORTED CASES OF MEASLES BRITISH COMMONWEALTH AIR TRAINING PLAN (BCATP) IN CANADA ³⁰			U.S. ARMY ^{31,32}	
	ROYAL NAVY	ROYAL AIR FORCE	ARMY UK ADMISSIONS TO HOSPITAL	RAF IN CANADA	RAAF IN CANADA	RNZAF IN CANADA	US ARMY IN US	US ARMY HOSPITAL ADMISSIONS TOTAL OVERSEAS
1939	0.7	1.8	1.11				1.4	
1940	0.8	2.1	0.55				3.7	
1941	1.2	1.7	0.49	5.5	24.6	15.8	9.8	
1942	0.4	0.7	0.19	5.5	10.6	11.2	4.5	1.58
1943	0.8	1.1	0.57	4.3	3.9	4.4	5.7	0.80
1944	0.3	0.6	0.34	7.5	4.7	6.3	2.7	0.57
1945	0.4	0.5	0.40				0.9	0.42

Having accepted the diktat of the U.S. Secretary of War Henry L. Simson, CAJ remained at Harvard^{1,2,3,11,12,13,24,25,26,27}. He thereafter did much valuable work on the prevention of epidemics. During World War I the incidence of measles in U.S. troops in Europe had been high²⁸, but during World War II it was low (Table 1). Geoffrey Keynes and the Lionel Whitbys closely collaborated on aspects of blood transfusion including the administration of immune serum in the treatment of measles^{33,34,35,36,37}. The generations-long friendship of the Stimsons and Janeways co-existed with deep experience. CAJ's father Thomas, as Head of Medicine at Hopkins, resigned shortly before his death in

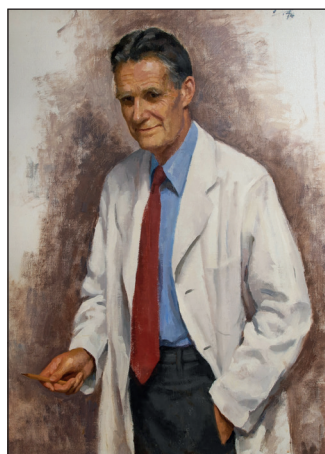


Figure 1

Charles Alderson Janeway, M.D. (1909-1981), Physician in Chief, Children's Hospital, Boston 1946-1976, and Thomas Morgan Rotch Professor of Pediatrics, Harvard Medical School. Oil on canvas, 32" x 40", 1975, by George V. Augusta, Jr. (1922-2012). From the portrait collection of Boston Children's Hospital, and reproduced with permission of the artist's estate.

1917, to advise the then U.S. Surgeon General. During World War I he attained the rank of Major and Henry Stimson that of Colonel in U.S. Artillery. John F. Enders had attained the rank of Ensign as a U.S. pilot in World War I.

Late in 1941, after Pearl Harbor, Harvard's Moseley Professor of Surgery, Elliott Carr Cutler, Harvey Cushing's

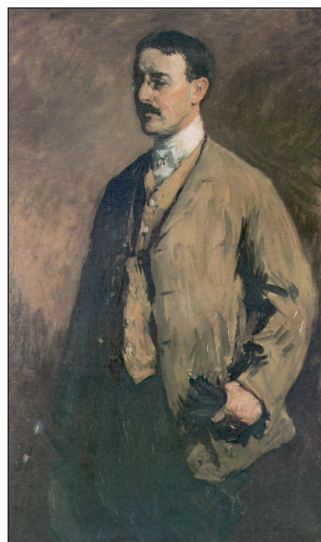


Figure 2

Colonel Henry Lewis Stimson (1867-1950), U.S. Secretary of War under President William H. Taft (1911-1913), and later under FDR (1940-1945), by Julius G. Melchers (1860-1932), 1913. Oil on Canvas, 51.5" x 30.74", from the collections of the Center of Military History, Washington, DC. Stimson was appointed Governor-General of the Philippines by President Calvin Coolidge in 1927 and served until 1929, when he was appointed U.S. Secretary of State. In 1939, he was reappointed to his former post of Secretary of War by FDR.

successor as commandant of Harvard's 5th U.S. Army General Hospital^{2,3,37} had announced that CAJ would be his Assistant Director and Head of Pathology. This appointment was vetoed by the U.S. Secretary of War, Yale graduate, Henry L. Stimson, who ordered that CAJ should stay at Harvard and continue his work on the fractionation of human blood and the gamma globulins. Stimson and CAJ were both elected to Skull and Bones, "The inner circle of Yale good-fellowship", while undergraduates at Yale¹⁴ (Fig.1) (Fig.2).

During the U.S.'s engagement in World War I there were 2,370 deaths of enlisted soldiers in the United States and Europe attributed to measles³⁸. In World War II, by contrast, even with a quadrupled pool of military personnel for twice the time, the corresponding mortality figure was reduced to 33 deaths^{32,38}. The advice to the U.S. Secretary of War Stimson from Enders and CAJ on prevention and treatment was very effective, as was their close collaboration with Geoffrey Keynes and the Whitbys for United Kingdom troops, airmen and Allied Navies^{29,35,36,37} (Table 1).

Gamma globulin (human immune serum globulin) obtained as a product of human plasma fractionation was an effective means of prevention or amelioration of measles^{11,12,13}. Measles never became a serious military problem during World War II^{29,30,31,32,38} (Table 1).

SEQUELAE: THE LEGACY OF JOHN ENDERS

In 1959 CAJ recruited my wife from St. George's Hospital London to be Sidney Farber's intern and later to work in the John Enders Building opened in 1972 at Harvard's Children's Hospital in Boston^{1,39}.

John Enders, trained by Zinsser^{40,41,42,43,44,45}, started in 1939 with cultivated human renal cells to allow production of more renal cells to propagate measles virus in quantity⁴⁶. The Edmonston-Enders virus strain is still used in standard measles, mumps and rubella vaccine (MMR)^{47,48,49,50}. The wide-spread use of the Enders Measles vaccine led to the



UMJ is an open access publication of the Ulster Medical Society (<http://www.ums.ac.uk>).

The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

United Kingdom, the United States and a number of other countries being declared measles-free^{51,52}. The World Health Organization (WHO) defines elimination of measles as “the interruption of measles transmission in a defined geographical area that has lasted at least 12 months”⁵³. Because of its high infectivity, “the herd protection threshold for measles is the highest of all vaccine-preventable diseases and varies in different settings ranging from 89% to 94%”⁵³. Now in 2020, Boston has registered two confirmed cases of measles in the past 4 months⁵⁴ (Fig. 3). Air travel to both the U.K. and U.S. warrants closer monitoring: Koplick spots are easily recognizable. The WHO has reported global annual incidence of measles of approximately 6,733,000 cases resulting in 109,638 deaths as recently as 2017^{53,62,63}. Complications such as blindness, encephalitis, pneumonia, as well as death, are more frequent among malnourished or vitamin-A deficient children, or those with immune systems weakened by HIV/AIDS or other causes^{51,52,62,63}. Measles may disrupt the function of F protein and result in neurological sequelae including “primary measles encephalitis, acute post measles encephalitis, subacute sclerosing panencephalitis (SSPE) and measles inclusion body encephalitis (MIBE)”⁶⁴.

WHO has reported that during the period 2000–2017, measles vaccination prevented an estimated 21.1 million deaths worldwide, a decline of 80 percent during that time

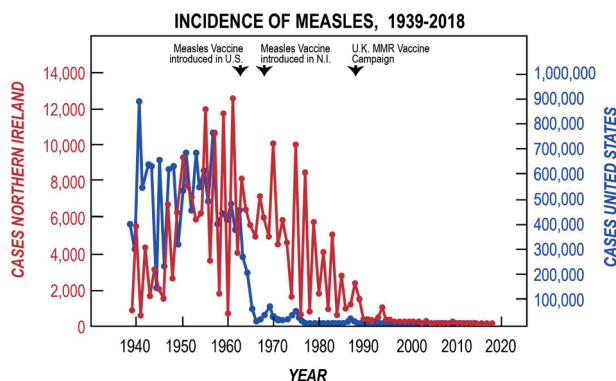


Figure 3

Incidence of Measles in Northern Ireland and the United States, 1939–2018. The incidence of measles in Northern Ireland⁵⁵ (red) and the United States^{56,57,58,59} (blue), reflects natural patterns of outbreaks and acquired immunity prior to the implementation of vaccination programs in 1963 in the U.S.⁶⁰ and in 1968 in Northern Ireland⁶¹. In Northern Ireland, the steepest decline in reported cases occurred after the introduction in 1988 of the combined measles-mumps-rubella (MMR) vaccine given at age 15 months⁶¹. This was followed by a UK-wide campaign for vaccination of all school children in 1994⁶¹. More recently in Northern Ireland, as in the U.S., cases are mostly “imported” by air-travel^{60,61}.

period⁶². As of 2017, about 85 percent of children worldwide received one dose of measles vaccine by 12 months of age, but two doses are recommended, since approximately 15 percent of children do not develop immunity after the first dose. WHO estimates that 67 percent of children received a second dose of measles vaccine. At the same time, 8.1 million

or 39 percent, of the 20.8 million infants not receiving at least one dose of vaccine, were in India, Nigeria and Pakistan⁶², where clinical vitamin A deficiency remains an ongoing public health concern⁵.

While WHO has reported an 88 percent global decrease in incidence of measles during the period 2000–2016, from 145 to 18 cases per million persons, by 2019 the incidence had risen again to 120 cases per million, its highest rate since 2001⁶⁵. Sixty-two percent of countries reporting in 2019 included viral genotype information. The WHO reported that twenty out of twenty-four recognized measles genotypes could be eliminated by vaccination⁶⁵. Global estimates of measles mortality increased nearly 50 percent between 2016, which had the lowest rates recorded since 2000, and 2019. Failure to vaccinate is recognized as the main cause of resurgence⁶⁵. The 2020 coronavirus pandemic has led to further decreases in vaccination and surveillance⁶⁶.

BELFAST AND BOSTON

The late Distinguished Professor Emerita of Neuropathology Dame Ingrid Allen (Fig. 4) and her colleagues, including Professor Bertus K. Rima of the Center for Experimental Medicine, Queen’s University Belfast, identified the primary cell types infected with measles virus as those of the immune system—lymphocytes, macrophages and dendritic cells. In addition, they identified a small number of infected epithelial cells⁶⁷. This group also studied the role of the F-gene as a major determinant of neurovirulence⁶⁷.



Figure 4

Professor Dame Ingrid Allen (1932–2020), oil on canvas, 108 cm x 93.5 cm, No. QUB 6, by Tom Hallifax (1965–). From the collection of the Naughton Gallery, Queen’s University, Belfast and reproduced with permission.

Professor Allen established the Regional Neuropathology Service for Northern Ireland in 1972 and served as its first leader. In 2006 she began a review of Pathology Services in Northern Ireland which led to the establishment of the Northern Ireland Pathology Network⁶⁸. Post-measles immunosuppression and its long-term immunologic sequelae were elucidated. Measles vaccination (MMR), using Enders’ attenuated Edmonston strain aids prevention of all infectious disease and promotes “polymicrobial herd immunity”^{69,70}. Recent work by Michael J. Mina, now at Harvard University, and his U.S. and international colleagues, demonstrates that measles causes “elimination of 11 to 73% of the antibody repertoire across individuals”^{69,70}. The impairment of immune cells increases the risk of secondary infection

leading to many of the deaths attributable to measles^{69,70}. Adaptive immunity will also play a role in determining response to coronavirus disease vaccines⁷¹.

TUTORING

My Clare College Physiology tutor, E.N. Willmer, FRS, has described in detail Enders' tissue culture technique^{46,72}. Willmer opined that herd immunity for measles would require the immunity of at least 96 percent of the population. This prediction to me in 1954 occurred in the Fellows' Garden, that Willmer designed and supervised. The Cam flows past.

ACKNOWLEDGEMENTS

The authors wish to thank Ms. Joy Murphy, Health Protection Surveillance Officer, Information Section, BBV/STI/VPD/I&V, Public Health Agency, Northern Ireland, for providing historical data on the incidence of measles in Northern Ireland. We wish to thank Mr. Ben Crothers, Curator and Collections Manager, the Naughton Gallery, Queen's University, Belfast, for reproduction of the portrait of the late Professor Dame Ingrid V. Allen. The authors wish to thank Mr. Philip Augusta for permission to reproduce the portrait of Professor Charles A. Janeway painted by his late father. The authors wish to thank Ms. Alina J. Morris, MLIS, Archives Program Manager, and Ms. Cindy L.Y. Chow, Executive Assistant to Dr. Gary R. Fleisher, Department of Medicine, Boston Children's Hospital, for assistance. The authors also wish to thank Professor Tweed Roosevelt, University Professor, Long Island University, for his insightful suggestions and historical perspective.

REFERENCES

- Hedley-Whyte J. Epidemic jaundice: Harvard's 5th General Hospital at Musgrave Park in World War II. *Ulster Med J.* 2005;**74**(2):122-5.
- Cutler EC. Base Hospital No. 5. *Harvard Alumni Bull.* 1941;**43**(18):1045-8.
- Cutler EC. Fifth General Hospital (Harvard University Unit), U.S. Army. *Harvard Med Alumni Bull.* 1942;**16**(2): 27-9.
- Hedley-Whyte J, Milamed DR. Tuberculous scrofula: Belfast experience. *Ulster Med J.* 2011;**80**(2):97-103.
- Hedley-Whyte J, Milamed DR. Aspects of vitamin A. *Ulster Med J.* 2009;**78**(3):171-8.
- Hedley-Whyte J, Milamed DR. Asbestos and shipbuilding: Fatal consequences. *Ulster Med J.* 2008;**77**(3):191-200.
- Panum PL. Observations made during the Epidemic of Measles on the Faroe Islands in the Year 1846. [Internet]. *Bibliothek for Laeger*, Copenhagen, 3R, 1847:**1**: 270-344. [cited 2019 Dec 11] Available from: <http://www.med.mcgill.ca/epidemiology/courses/EPIB591/Fall%202010/mid-term%20presentations/Paper9.pdf> [Accessed April 2021].
- Hume EM, Krebs HA. *Vitamin A Requirement of Human Adults: an experimental study of vitamin A deprivation in man. A report of the Vitamin A Sub-Committee of the Accessory Food Factors Committee.* Medical Research Council. Special Report Series No. 264. London: HMSO; 1949.
- Enders JF. Measles virus. Historical review. Isolation and behavior in various systems. *Am J Dis Child.* 1962;**103**:282-7.
- Hedley-Whyte J, Milamed DR. International contributions toward the conquest of polio. *Ulster Med J.* 2019;**88**(1):47-54.
- Haggerty RJ, Lovejoy FH Jr. *Charles A. Janeway: pediatrician to the World's Children.* Boston: Children's Hospital, Harvard Medical School, Harvard University Press; 2007.
- Ordman CW, Jennings CG, Jr., Janeway CA. Chemical, clinical and immunological studies on the products of human plasma fractionation. XII. The use of concentrated normal human serum gamma globulin (human immune serum globulin) on the prevention and attenuation of measles. *J Clin Invest.* 1944;**23**(4):541-9.
- Janeway CA, Rosen FS, Merler E, Alper CA. *The Gamma Globulins.* New England Journal of Medicine Medical Progress Series. Boston: Little, Brown and Co.; 1967. p.104-6.
- Current RN. *Secretary Stimson. A study in statecraft.* New Brunswick, NJ: Rutgers University Press; 1954. p. 8.
- Stimson HL, Bundy M. *On Active Service in Peace and War.* New York: Octagon Books; 1971.
- Stimson HL. *My Vacations.* New York: Privately printed; 1949 [Available from the collections of the Harvard University Library, inscribed by the author to James B. Conant, President, 1933-1953].
- The President's case. *Red Cross Notes* [Internet]. 1901; S3n9: 191-6. [cited 2020 Jan 27] Available from: <http://mckinleydeath.com/documents/journals/RCNotes3-9.htm>. Accessed April 2021.
- Badger TL, Ayvazian LF. Clinical observations on the pathogenesis of tuberculosis: From a 15 year follow-up of 745 nurses. *Trans Am Clin Climatol Assoc.* 1948;**60**:12-28.
- Badger TL, Ayvazian LF. Tuberculosis in nurses: clinical observations on its pathogenesis as seen in a 15 year follow-up of 745 nurses. *Am Rev Tuberc.* 1949;**60**(3):305-31.
- Rycroft BW. Night vision in the Army. *Brit Med J.* 1942;**2**(4271):576-7.
- Rycroft BW. Ophthalmology in the B.N.A. & C.M. Forces. *Br J Ophthalmol.* 1945;**29**(11):594-607.
- Duke-Elder WS. *Text-Book of Ophthalmology.* St.Louis, MO: C.V. Mosby Co; 1941-2. Vol. 1, p.982-3; vol. 2, p.1422-3, 1544-6; vol.3, p.2149-50, 2673.
- Rutherford Morison J. *BIPP Treatment of War Wounds.* London: Henry Frowde, Hodder and Stoughton; 1918. p.10-13.
- Janeway CA. *Papers of Charles Alderson Janeway.* 1940-1963 (inclusive). Harvard University. Countway Library of Medicine, Center for the History of Medicine. GA.42.25. Correspondence file.
- Heyl JT, Gibson JG, Janeway CA, Shwachman A, Wojcik L. Studies on the plasma proteins. V. The effect of concentrated solutions of human and bovine serum albumin on blood volume after acute blood loss in man. *J Clin Invest.* 1943;**22**(6):763-73.
- Janeway CA. Blood and blood derivatives—a new public health field. *Am J Public Health Nations Health.* 1946;**36**(1):1-14.
- Janeway CA. Use of concentrated Human Serum gamma-globulin in the prevention and attenuation of measles. *Bull NY Acad Med.* 1945; **21**(4):202-22.
- Shanks GD, Hu Z, Waller M, Lee SE, Terfa D, Howard A, et al. Measles epidemics of variable lethality in the early 20th century. *Am J Epidemiol.* 2014;**179**(4):413-22.
- Mellor WF, editor. *Casualties and Medical Statistics.* Ellis FP. The Royal Naval Medical Services. Mayne HG. The Army Medical Services. Welch S.C.R. The Royal Air Force Medical Services. London: Her Majesty's Stationery Office; 1972. p.17, 22, 27,32,37,42,47,148, 537.
- Feasby WR, editor. *Official History of the Canadian Medical Services 1939-1945.* Vol. 1. Organization and Campaigns. Ottawa: Edmond Coutier CMG, AO; 1956. p.422.
- Stokes J, Jr. Chapter V. Measles. In: Coates JB, Jr., editor. *Medical Department. United States Army. Preventive Medicine in World War II, Vol. IV. Communicable Diseases Transmitted chiefly Through Respiratory and Alimentary Tracts.* [Internet]. Washington, D.C.: Office of the Surgeon General; 1958. p.129-34. [Cited 2020 Feb 6] Available from: <https://history.amedd.army.mil/booksdocs/wwii/PM4/default.htm> [Accessed April 2021].
- Reister FA. *Medical Statistics in World War II.* Washington, DC: Office of the Surgeon General. Medical Department, US Army; 1975. Table 29b. p.518-519.



UMJ is an open access publication of the Ulster Medical Society (<http://www.ums.ac.uk>).

The Ulster Medical Society grants to all users on the basis of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence the right to alter or build upon the work non-commercially, as long as the author is credited and the new creation is licensed under identical terms.

33. Keynes G. *Blood Transfusion*. London: Henry Frowde and Hodder & Stoughton; 1922. p.62.
34. Terrien E. Transfusion of blood in malignant measles. *Bull Soc Méd des Hôp*. 1919;**43**:1134-6.
35. Brewer HJ, Ellis R, Greaves RI, Keynes G, Mills FW, Scott RB, *et al*. *Blood Transfusion*. Bristol: John Wright & Sons Ltd. 1949. p.107-9, 195.
36. Hedley-Whyte J, Milamed DR. Lobar pneumonia treated by Musgrave Park physicians. *Ulster Med J*. 2009;**78**(2):119-28.
37. Hedley-Whyte J, Milamed DR. Our blood your money. *Ulster Med J*. 2013;**82**(2):114-20.
38. Kneeland Y, Jr., editor. Chapter 1. Respiratory disease. In: Coates JB, Jr., editor. Medical Department. *United States Army. Internal Medicine in World War II. Vol. II. Infectious Diseases*. [Internet]. Washington, D.C.: Office of the Surgeon General: p.32-4. [cited 2020 Feb 6]. Available from: <https://history.amedd.army.mil/booksdocs/wwii/infectiousdisvolii/chapter1.htm> [Accessed April 2020].
39. Hedley-Whyte ET. On being a pathologist: how does one plan a career, or does one? *Hum Pathol*. 2008;**39**(9):1269-74.
40. Zinsser H. *As I remember him: the biography of R.S.* Boston: Little, Brown: 1964. (originally published 1939).
41. Zinsser H. An immunological consideration of the virus problem. *Military Surgeon*. 1936;**79**:171-182.
42. Zinsser H. On the nature of virus agents. *Am J Public Health Nation's Health*. 1937;**27**(11):1160-3.
43. Zinsser H, Enders JF. Variation in the susceptibility of guinea pigs to reversed passive anaphylaxis. *J Immunol*. 1936;**30**(4):327-37.
44. Zinsser H, Fothergill LD, Enders JF. *Immunity. Principles and application in medicine and public health*. (5th ed of *Resistance to Infectious Diseases*). Chapter XXIX. Applied immunology in some virus diseases. Measles (Morbilli). New York: MacMillan; 1939. p.750-7.
45. Enders JF. Chemical, clinical and immunological studies on the products of human plasma fractionation. X. The concentrations of certain antibodies in globulin fractions derived from human blood plasma. *J Clin Invest*. 1944;**23**(4):510-30.
46. Enders JF, Peebles TC. Propagation in tissue cultures of cytopathogenic agents from patients with measles. *Proc Soc Exp Biol Med*. 1954;**86**(2):277-86.
47. Enders JF. Vaccination against measles. *Aust J Exp Biol Med Sci*. 1963;**41**(Suppl):467-89.
48. Enders JF, Kempe CH, Krugman S, Stokes J Jr. Evaluation of measles virus. *JAMA*. 1962;**180**:680.
49. Mitus A, Holloway A, Evans EA, Enders JF. Attenuated measles vaccine in children with acute leukemia. *Am J Dis Child*. 1962;**103**:413-8.
50. Katz SL, Enders JF, Holloway A. Use of Edmonston attenuated measles strain. A summary of three years' experience. *Am J Dis Child*. 1962;**103**:340-4.
51. World Health Organization. Framework for verifying elimination of measles and rubella. [Internet]. WHO. *Weekly Epidemiological Record* 2013;**88**(9):89-100. [cited 2020 Feb 3] Available from <https://www.who.int/wer/2013/wer8809.pdf> [Accessed April 2021].
52. World Health Organization. *Global Measles and Rubella Strategic Plan 2012-2020*. [Internet]. Geneva: WHO; 2012. [cited 2020 Jan 28]. Available from: https://apps.who.int/iris/bitstream/handle/10665/44855/9789241503396_eng.pdf;jsessionid=9D1A10C37C67C3A7E652BAEC65F1D6D6?sequence=1 [Accessed April 2021].
53. World Health Organization. Measles vaccines: WHO position paper – April 2017. [Internet] *Weekly Epidemiological Record*. 2017;**92**(17):205-28. [cited 2020 Feb 5]. Available from: <https://www.who.int/wer/2017/wer9217/en/> [Accessed April 2021].
54. McDonald D. Northeastern student diagnosed with measles. *Boston Globe*. 2020 January 10:B4.
55. Public Health Agency, Northern Ireland. Data provided to the authors upon request (see acknowledgements).
56. Historical Summary Tables covering the Period 1939-1988. Table 1. Notifiable diseases – Summary of reported cases, United States, 1979-1988. Table 3, 1969-1978, Table 4, 1959-1968, Table 5, 1949-1958 Table 6, 1939-1948. *Morbidity and Mortality Weekly Report*. 1988;**37**(54):51-56.
57. Table 8, Reportable cases of notifiable diseases -- United States, 2005-2012, Table 9, Reported cases of notifiable diseases – United States, 1997-2004, Table 10. Reported cases of notifiable diseases – United States, 1989-1996. *MMWR* 2014;**61**(53):105,107,109.
58. *MMWR: Summary of Notifiable Infectious Diseases*, 1993-2015. https://www.cdc.gov/mmwr/mmwr_nd/index.html (Accessed 30 January 2020).
59. U.S. Centers for Disease Control. *Nationally Notifiable Infectious Diseases and Conditions. United States: Annual Tables. 2016-2018*. https://wonder.cdc.gov/nndss/nndss_annual_tables_menu.asp (Accessed 30 January 2020).
60. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013. Summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report (MMWR)* 2013;**62**(4):1-34 and erratum to p.8.
61. Smithson R, Irvine N, Hutton C, Doherty L, Watt A. Spotlight on Measles 2010: Ongoing measles outbreak in Northern Ireland following an imported case, September –October 2010. *Euro Surveill*. 2010;**15**(43):19698. doi:10.2807/ese.15.43.19698-en. www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19698 (accessed November 14, 2019).
62. World Health Organization. *Newsroom. Fact Sheets. Detail. Measles*. [Internet]. Geneva: WHO; 2019 December 5. [cited 2020 January 2020]. Available from: <https://www.who.int/news-room/fact-sheets/detail/measles> [Accessed 20 January 2020].
63. World Health Organization. *News. New measles surveillance data for 2019*. [Internet]. Geneva: WHO; 2019 May 15. [cited 2020 Jan 30]. Available from: <https://www.who.int/immunization/newsroom/measles-data-2019/en/> [Accessed April 2021].
64. Patterson MC. Neurological complications of measles (rubeola). *Curr Neurol Neurosci Rep*. 2020;**20**(2):1-8. doi: 10.1007/s11910-020-1023-y.
65. Patel MK, Goodson JL, Alexander JP, Jr., Kretsinger K, Sodha SV, Steulet C, *et al*. Progress toward Regional Measles Elimination—Worldwide, 2000-2019. *Morbidity and Mortality Weekly Report*. 2020; **69**(45):1700-5.
66. O'Brien K. Report from the director of IVB: building back better for immunization in a COVID-19 world. [Internet]. Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization, October 5-7, 2020, Geneva, Switzerland. [cited 2020 October 20]. Available online from: https://www.who.int/immunization/sage/meetings/2020/october/SAGE_Slidedeck_Oct2020-Web.pdf?ua=1 [Accessed April 2021].
67. Allen IV, McQuaid S, Penalva R, Ludlow M, Duprex WP, Rima BK. Macrophages and dendritic cells are the predominant cells infected in measles in humans. *mSphere*. 2018; **3**(3):e00570-17. doi: 10.1128/mSphere.00570-17.
68. The Faraday Institute. Prof. Dame Ingrid Allen. Cambridge, UK: The Faraday Institute for Science and Religion. [cited 2020 Nov 20]. Available from: <https://www.faraday.cam.ac.uk/about/people/prof-dame-ingrid-allen/> [Accessed April 2021].
69. Mina MJ, Metcalf CJ, de Swart RL, Osterhaus AD, Grenfell BT. Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. *Science*. 2015;**348**(6235):694-9.
70. Mina MJ, Kula T, Leng Y, de Vries RD, Knip M, Siljander H, *et al*. Measles virus infection diminishes preexisting antibodies that offer protection from other pathogens. *Science*. 2019;**366**(6465):599-606.
71. Saad-Roy CM, Wagner CE, Baker RE, Morris SE, Farrar J, Graham AL, Levin SA, Mina MJ *et al*. Immune life history, vaccination, and the dynamics of SARS-CoV-2 over the next five years. *Science*. 2020; **370**(6518):811-8.
72. Rapp F, Melnick JL Chapter 4.. Cell, tissue and organ cultures in virus research, In: Willmer EN, editor. *Cells and Tissues in Culture. Methods, Biology and Physiology*. Vol 3. London: Academic Press; 1966. p.263-316.

