Papers and Originals

Mass Immunization in the Control of Infectious Disease*

D. THOMSON,† C.B., M.D., M.R.C.P., D.P.H.

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In 1518, when the Royal College of Physicians was founded, plague was rife, and the resulting sense of emergency partly explains why a new organization of physicians was set up. Henry VIII often consulted the College, and in 1529, being excluded from London by a fresh outbreak, the King asked for advice on measures to be taken to control the infection. Arising from this the Privy Council instituted the registration of cases and issued Bills of Mortality.

Dr. Gavin Milroy (1805-86), the founder of these lectures, was keenly interested in the great infections of his time. This interest was roused by his experiences when Superintendent Medical Inspector of the General Board of Health and on his several trips overseas. Notable among those was his stay in the Crimea from 1855 to 1856 as a member of a three-man sanitary commission appointed to advise on the health of the troops, when over a sixth were suffering from cholera, typhoid, dysentery, or typhus. The conclusion reached was that the spread of disease was due to bad hygiene. Soon the incidence of sickness fell, although this may have been brought about more by the improvement in the weather than by the implementation of the commission's recommendations. Florence Nightingale had no doubts, and with characteristic forthrightness the tempestuous reformer commented that the commission's work "saved the British Army." Their views had been in line with hers, that "there are no specific diseases. There are specific disease conditions."

During the remaining 30 years of his life Milroy took a particular interest in the part played by contagion in epidemics. At the end of his last paper, delivered to the Epidemiological Society of London, he comments: "I only

remark in conclusion that exanthemata are diseases more of persons than of places." No doubt he would have been fascinated by the successful control of infectious diseases brought about by medical advance and State organization. So complete has this been that the middle of the twentieth century can be regarded as the end of one of the most important social revolutions in history, marked by the greatest human achievement so far in the control of our environment.

Foundations

From mediaeval times the State has tried to check epidemics. In 1346, when leprosy was present in the City of London, Edward II ordered "that diligent search be made for lepers in order that they may be immediately expelled." Because of plague the Court fled from London in 1518, and was resident successively in Berkshire and Oxfordshire. Then Sir Thomas More charged the Mayor of Oxford, in the King's name, "that the inhabitants of those houses that be, or shall be, infected, shall keep in, put out wisps, and bear white rods, as your Grace devised for Londoners." Elizabeth I, when she sought refuge in Windsor during the epidemic of 1564, instituted much sterner measures. She decreed that no wares be brought into the town from London, and that a gallows be erected in the market-square to hang all who came from the capital.

In Milroy's time isolation and quarantine were still the main measures used to control infection, although there was increasing questioning of their efficacy. During the age-long controversy on the communicability of disease the College of Physicians remained vigorously anticontagionist; this despite the opposition of certain notable Fellows. Few of those were so forceful in expressing disagreement as Thomas Willis, who became Professor of Natural Philosophy at Oxford and gave his name to the arterial anastomosis at the base of the brain.

Dr. Gavin Milroy.

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† Treasury Medical Adviser, lately Deputy Chief Medical Officer, Ministry of Health.

Willis first described typhus as "the new disease" in 1643, and during the controversy on its mode of spread he retorted sharply, "but if anyone be yet obstinate, and will not believe it contagious, let him go near and try."

Before reviewing the advances made in the control of infectious disease it is instructive to recall the state of the public health in 1876, when the original draft of the memorandum establishing these lectures was penned. Then the average expectation of life in England and Wales for a male at birth was 41 years and for a female 43 years, in contrast to 68 years for a male child and 74 for a female today. A third of all deaths were due to infectious disease, compared with 1.2% in 1965. The number of deaths from infections in 1876 compared with those in 1940 and 1965 are shown in Table I.

TABLE I.—Deaths from Infective Diseases: England and Wales

Year:	1876	1940	1965
Population:	24,244,010	39,899,000	47,762,800
Infective diseases*	159,293	48,047	4,138
Smallpox	2,408	0	0
Diphtheria	3,000	2,466	0
Tetanus		109	21
Whooping-cough	10,556	678	16
Tuberculosis	62,633	27,871	2,282
Poliomyelitis (including late effects)		159	19
Influenza	203	11,420	814
Measles	9,971	855	115
Scarlet fever	16,893	152	1
Chickenpox	109	10	13

* Includes tuberculosis and influenza, excludes venereal and parasitic diseases.

Small wonder that William Farr, in the 35th Annual Report to the Registrar-General published in 1875, wrote pessimistically: "In quenching the flames at one point the good work is begun but is not ended. Can infectious disease of all kinds never be quenched?" He went on half-heartedly to further question: "Can lifetime be prolonged by the knowledge of the causes that cut it short, or by means within a nation's power?" Nevertheless, in retrospect, that can be recognized as the time when the foundations for a great advance in the nation's health were being laid. Indeed, 1876 may be regarded as an "annus mirabilis" in the control of infectious diseases.

By a remarkable coincidence, in the same month as Milroy jotted down his initial thoughts on these lectures, Robert Koch, a district physician in Wollstein, who had been investigating the development of the anthrax bacillus, was invited by the University of Breslau to demonstrate his discoveries. W. H. Welch, the father of United States bacteriology, was a student there at the time, and he told of Koch being closeted for long with members of the medical faculty. Then suddenly Welch's teacher, Professor Cohnheim, burst into the laboratory crying out, "This is the greatest discovery ever made in bacteriology." Soon afterwards Louis Pasteur revealed the principles of acquired immunity and the development of practical methods of producing such by artificial means. This prompted William Osler to comment: "Before him Egyptian darkness; with his advent a light that lightens more and more as the years give us ever fuller knowledge."

Fortunately it was a climacteric in spheres other than that of medicine. For, to take advantage of these advances, it was necessary to have the means of organizing effort and a receptive and well-informed population. The preliminaries towards the achieving of these prerequisites coincided with the great discoveries in bacteriology. In 1872 Disraeli inscribed upon his banner the war-cry, "Sanitas Sanitatum Omnia Sanitas," and spoke of the health of the people as "the real foundation on which all happiness and all their power as a State depend." In 1875 a Public Health Act was passed which recognized that the care of the public health was a national responsibility. Since then the maintenance of health has become progressively a vital political and economic force in this country. Further, an Act of the following year paid heed to the centuries-old

advice of Plato and made education compulsory for all children. Thus was the task of preventive medicine made much easier.

Early Attempts to Control Smallpox

Long before these medical and social advances attempts had been made to control smallpox by means other than isolation and quarantine, and early in the 19th century the State took an interest.

Soon after the first epidemic in 1628 it had been observed that an attack of the disease gave rise to immunity, and this was widely accepted in the 17th century. One reads of the diarists Samuel Pepys and John Evelyn calling, on 15 September 1685, on Mrs. Graham, Maid of Honour to the Queen, in Bagshot, on their way to Portsmouth, and Evelyn's comment: "Her eldest son was now sick of the smallpox but in a likely way to recover, and others of her children ran about and among the infected, which she said she let them do on purpose that they might whilst young pass that vital disease she fancied they were to undergo one time or other, and that this would be for the best." This must have appealed particularly to Evelyn, for when he was ill in Geneva in 1646 he was bled, leeches, and purged before the diagnosis of smallpox was made, and he plaintively noted in his diary, "God knows what this would have produced if the spots had not appeared."

On 17 April 1721 inoculation was mentioned by Dr. Walter Harris, who practised in Constantinople, in a lecture to the College of Physicians, the protection having probably been introduced into Turkey from Greece. Such prophylaxis did not prove to be without hazard, and fell into disrepute. The publication in 1796 by Edward Jenner of his monograph on vaccination with cowpox introduced a more dependable method. Despite the immunity given by vaccination there occurred in 1839 this country's greatest epidemic. It raged for three years, and in 1840 the State first intervened to try to control an infection by vaccination. Legislation enabled the poorer classes to have their children vaccinated at the ratepayers' expense and prohibited the practice of inoculation. Thus was established the prototype of the vaccination and immunization campaigns of recent years.

Difficulties in Achieving Mass Protection

It was in 1940, exactly 100 years after its initial attempt to control communicable disease by vaccination, that the State launched another prophylactic campaign, in this case to check the spread of diphtheria. Mass immunization against whooping-cough, tuberculosis, and poliomyelitis followed. In those later campaigns the century-old difficulties which had marked the attempts to obtain mass protection against smallpox were evident—namely, the varying efficacies of the antigens used; the reluctance of many to take advantage of the protection; and the possibility of complications bringing the campaigns into disrepute.

The need for uniformly effective antigens was early recognized. In 1808 a national vaccine establishment was set up which collected lymph that vaccinators had obtained from those vaccinated. In 1881 the Government set up an institute for the manufacture and distribution of calf lymph, which existed until 1945. By the Act of 1898 lymph was issued free to vaccinators. The organization of national preventive measures was made much easier by the establishment in 1919 of a central controlling body—the Ministry of Health. The Medical Research Council was set up in 1920, and since then its expert committees have guided the Ministry on the scientific aspects of immunization. Soon after the establishment of these bodies it was recognized that the development of new prophylactics, notably against diphtheria, necessitated statutory control, and the Therapeutic Substances Act was passed in 1925. Under

its provisions the potency, sterility, and absence of toxicity of biological substances are ensured.

It has always proved more difficult to get the public to accept immunization than to produce a relatively safe and potent antigen. In 1853 vaccination against smallpox before the age of 3 months was made compulsory, but a high proportion of protected infants was not achieved. Eventually this led to the setting up of a Royal Commission in 1889 to inquire into the vaccination laws. Arising from its report an Act of 1898 allowed conscientious objectors to be excused vaccination. This was widely interpreted, and, except during epidemics, protection was sought by the parents of only a minority of infants. In 1946, the year of the passing of the National Health Service Act, the proportion of children under 12 months vaccinated was only 41.6%—half the ratio protected in 1898—and compulsory vaccination was discontinued. Before 1946 the national diphtheria immunization campaign, which was fully launched in 1941, had proved highly successful without compulsion. This arose from the realization that health education is one of the most important preventive measures. For the provision of the means of control fails unless there is individual and communal understanding of their use and acceptance of their value.

The success of the diphtheria immunization campaign has, in varying degrees, been repeated in those to control whooping-cough, poliomyelitis, and tuberculosis. The figures in Table II

TABLE II.—Rates of Protection—England and Wales—1965

	National Level (%)	Highest L.H.A. Level (%)	Lowest L.H.A. Level (%)
Smallpox:			
Proportion under 2 years vaccinated ..	33	77	10
Diphtheria:			
Children born in 1964 immunized ..	71	89	43
Whooping-cough:			
Children born in 1964 immunized ..	70	88	36
Poliomyelitis:			
Children born in 1964 vaccinated ..	65	88	39

show, however, that much can yet be achieved. There is a wide range of protection among the various local health authorities, with many of the great industrial centres having a disappointing level.

The history of smallpox shows that no vaccine is absolutely safe. Over a century ago variolation fell into disrepute when it was realized that 2% to 3% died from the procedure. During the decades when smallpox was a major health hazard the occasional complication was rarely recognized, and, if so, it was considered a small price to pay for a national protection. But as the infection waned there was increasing appreciation of such complications and questioning whether they represented too high a price for warding off a risk which was ever diminishing. To date, complications of all prophylactic procedures have been comparatively few, and have been judged to be far outweighed by the protection achieved. Incidents in other countries giving rise to a number of deaths, which marked the early stages of mass protection against diphtheria, tuberculosis, and poliomyelitis, were found to be due to faulty preparation of the antigen.

None the less, there is the need for vigilance and for the assessment of the value of mass protection as the incidence of the particular disease declines. The main factors which govern such an assessment are: (a) the frequency and severity of undesirable reactions; (b) the degree and duration of the protection; (c) the probability of exposure to infection; (d) the probability of contracting the disease as a result of exposure; (e) the nature and severity of the disease. It has to be accepted that a small number will react adversely to any antigen, probably because of an abnormality in their immunological defence system, either hereditary or induced by illness.

Accomplishments

Smallpox

The acceptance rate of vaccination in England and Wales in 1949 was 28%, which compares with an average of 36.8% over the previous decade. In 1965, by which time the second year of life was recognized as being safer than the first for primary vaccination, 33% of children under two years were protected, which compares with corresponding figures of 50%, 47%, 48%, and 70% for the years 1959 to 1962, when vaccination during the first 12 months of life was advocated. These acceptance rates, as well as demonstrating that persuasion can give at least as good results as legal compulsion, underline the difficulty of persuading mothers to have children vaccinated in the second year of life. Since reasonably complete statistics became available in 1951 almost 8½ million primary vaccinations and just over 4½ million revaccinations have been notified. During those 15 years there were 137 cases of smallpox in England and Wales, with 47 deaths. Of those who died 30 had never been vaccinated, 12 had been vaccinated at least 35 and mostly over 50 years previously, and in five cases vaccination at any time seemed doubtful.

The introduction of glycerinated calf lymph in the last years of the 19th century greatly diminished the risk of infection from contamination. The occasional cases of general vaccinia were still notified, and in 1922 neurological complications were recognized. Since then details of such have been collected and studied at the Ministry of Health. An analysis is given in Table III of data collected in the period 1951 to 1965 inclusive. Accepting a connexion with vaccination in all the deaths, the rate is only 5.4 deaths per million persons vaccinated, although 13.0 per million in infants. Still, vaccinia gives rise to more complications than any other biological product.

TABLE III.—Complications of Smallpox Vaccination, 1951–65

Total No. of Vaccinations	No. of Resulting Illnesses	Benign Generalized Vaccinia	Chronic Progressive Vaccinia	Generalized Vaccinia Associated with Eczema	Illness Affecting the Central Nervous System	Deaths to which Vaccination may have Contributed
13,096,779	563	346	14 (11)	52 (9)	128 (29)	(23)

Number of deaths shown in parentheses.

Primary vaccination of adults should be carried out only when there is a specific risk—for example, when the individual is exposed to smallpox, is travelling to an area where the disease is endemic, or is coming into contact regularly with the sick. Such persons should be revaccinated every three years. After successful vaccination there is little danger of the individual, if exposed, contracting smallpox for about 10 years, and immunity of some degree may last for more than 20 years. Protection is even greater against variola minor.

During this century the glycerinated lymph available for public vaccination has been derived from a single seed strain of "vaccinia" virus, the only substantial change being that from 1947 onwards sheep, and not as previously calves, have been used. The origin of the virus is obscure, but it is doubtful if it has come directly from variola. Freeze-dried vaccine is now obtainable which does not lose potency for several months at room temperature and for many years at +4° C. Recently field trials have tested the value of vaccination with tissue-culture preparations, and there is hope that once this method is improved the number of complications will decrease. The value of purified inactivated virus with adjuvant, given subcutaneously, is also likely to be investigated. Certainly there is need for an even more effective and safer vaccine, since, with increasing air travel and because in large parts of the world the infection is still endemic, the risk of smallpox being imported is ever with us.

The advice that all children should be vaccinated in early life has been criticized. But early protection ensures a much quicker response, with little risk of complications, when secondary vaccination is needed as a result of possible exposure to smallpox in later life. Opinion would almost certainly come to be decisively in favour of infant vaccination if there was a vaccine which produced little local reaction and less viraemia.

Diphtheria

In 1959 there was no death from diphtheria in England and Wales for the first time since notification was introduced 100 years before, when this country experienced its most severe epidemic, causing 10,184 deaths. Thirty-one years later von Behring and Kitasato showed how immunity could be obtained by injecting sublethal doses of living bacilli, and in 1913 von Behring, Schick, and Parke and his collaborators showed that toxin-antitoxin mixture produced a relatively safe and rapid immunity. From that time successful immunization against diphtheria dates.

In this country its introduction was comparatively slow, although by 1937 45% of pre-school children in Chester had been immunized, and the corresponding figure in Birmingham, Leeds, Manchester, Walsall, and Worcester was around 30%. By contrast, only 5.3% of such children in London had been protected, and in the country as a whole from 8% to 10%. Undoubtedly the efforts of individual medical officers of health helped to curb the infection locally, but they did not affect the national trend. It was only when the State intervened to marshal and direct forces that a decisive impact was made. It was calculated that previous to this 5% to 10% of children contracted diphtheria at some time, and of those 1 in 20 died.

The national campaign to control the infection developed fully in 1941. So successful was this that by the end of the war just over 60% of the child population had been immunized. In 1945 the number of diphtheria deaths in this age group had dropped to 584 compared with 2,390 in 1941. During the years 1942 to 1944 four out of every five children who had contracted diphtheria had not been immunized, and 29 out of 30 deaths were in non-immunized children, although the numbers of immunized and non-immunized were approximately equal. The eradication of diphtheria as an indigenous disease was well under way. Since the national campaign began in 1940 up to the end of 1965 17,754,923 children had received a full course of primary immunization and 11,007,711 had received a reinforcing injection. During the decade 1956 to 1965 there have been only 468 cases of diphtheria in England and Wales, with 33 deaths.

It has been shown that healthy carriers are to be found only around cases. The major danger now is that diphtheria, like smallpox, will be imported from abroad. This is emphasized by the fact that, while in England and Wales in 1965 there were only 25 cases, even in some European countries the position was much less satisfactory: in France there were 264 cases, in Germany 324, and in Italy 2,630. By contrast there were none in Norway and Sweden.

It has to be remembered that, while vaccination against smallpox becomes effective in a few days, immunity against diphtheria takes several weeks to develop. With the decrease in the number of those who develop immunity through sub-clinical infection the significance of immunization is greatly increased.

Whooping-cough

Mortality from whooping-cough has fallen sharply, but despite this its relative importance as a cause of death has increased. Notifications, introduced in 1940, have tended to

rise slightly in recent years, unlike those of the other communicable diseases. This may be partly due to other respiratory illnesses being wrongly classified, but there is evidence that the antigens used are not so effective as those which have succeeded in curbing smallpox and diphtheria. During the past decade, of the 414,197 cases notified 41,191 were in children under 1 year of age (9.9%); by contrast, of the 419 deaths from the infection 304 were in infants (72.5%). Whooping-cough is now 23 times more fatal in infants than in older children.

Mass immunization was introduced gradually. In 1953 83 local health authorities offered it, either singly or in combination with diphtheria, in the first six months of life. In 1961 official schedules of immunization recommending the use of combined diphtheria, tetanus, and pertussis vaccines were issued. Then all but one local health authority was providing immunization. During the period 1958–65 there were records of 4,889,416 children having been protected.

Just as pertussis vaccine has proved less effective than diphtheria antigen, so it has given rise to more complications. A large proportion of these are of a minor nature, represented by a local reaction or some slight fever within 24 hours. Much more serious are the rare cases of encephalopathy reported, marked by convulsions or, within half a dozen hours of injection, collapse and unconsciousness. Investigations are being carried out to determine the cause. The presence of foreign protein or of histamine or too many pertussis organisms has been suggested. Further vaccine should not be given if an earlier injection produced a sharp reaction, and not at all if the child is mentally deficient or has had convulsions, encephalitis, or related disease. Whooping-cough and immunization against it are likely to receive more attention in the future.

Tetanus

The danger of anaphylaxis following the giving of tetanus antitoxin serum has been increasingly recognized, and so routine immunization with tetanus toxoid has been encouraged. It was only after the publication of the official schedules of immunization in 1961 that all local health authorities in England and Wales adopted this procedure, generally in combination with diphtheria and pertussis antigens. An indication that this campaign is having an effect (although obviously the wider use of antibiotics has played a part) is that while in 1955 33 deaths were assigned to tetanus, in 1965 there were 21. Deaths in which tetanus was mentioned as a complication numbered 15 in 1955, but only 8 in 1965. There are good grounds for hope that such deaths can be eliminated before long.

Tuberculosis

B.C.G., which was introduced in 1921, was the first living bacterial vaccine to be used on a large scale in man in this country. A total of 54,239 healthy British children entered a Medical Research Council trial in 1950–52 and have been followed up. The trial showed that there was a 79% reduction in incidence. In 1949 B.C.G. had been offered to groups at special risk, mainly hospital nurses, medical students, and persons in close contact with cases of tuberculosis. Mass protection dates from 1953, when children in their 13th year were included. Since then vaccination has been extended to children aged 10 years and over, to students, and to those who may come into contact with patients suffering from tuberculosis. Freeze-dried B.C.G. vaccine, developed in this country, was introduced in April 1958, and is now the only antigen used.

During the campaign annual notifications of respiratory tuberculosis in England and Wales have declined from 38,410 in 1954 to 13,550 in 1965, of meningeal tuberculosis from 692 to 146, and of other forms from 4,139 to 2,404—a total decline of

63%. Deaths in 1965 numbered 2,282 compared with 7,897 11 years earlier—a reduction of 71%. Another indication of the improvement is that in 1953–4 tuberculosis caused 25.8 million days' (9% of total) absence from work in men, and by 1963–4 this had been reduced to 6.6 million days (2.3%). Apart from the occasional persisting local reaction and lymphadenitis, complications to B.C.G. have been significantly few. About 200 million persons throughout the world have now been vaccinated, with only 11 reported cases of general B.C.G. infection, presumably in those with abnormal susceptibility. Suppuration of regional lymph nodes occurs in one in 500 to one in several thousand cases, although the incidence is higher in newborn infants.

In England and Wales 4,529,004 had been given protection up to the end of 1965. This must have made a very considerable, if not measurable, contribution to the changed tuberculosis position of recent years. Now almost two-thirds of cases from respiratory tuberculosis are in men over 45 years, and in 1965 only 44 deaths from all forms occurred in those under 25.

Development of Virus Vaccine

During the century and a half from the introduction of Jennerian vaccination until the establishment of cell-culture technology in 1949 by Enders, Weller, and Robbins, tissues from the infected host animal and later from fertile eggs were used for the preparation of virus vaccines. The new methods ushered in the modern age of vaccine development, and have made possible control of all the important acute infectious diseases of viral aetiology.

Poliomyelitis

The first beneficial result of Enders's discovery was in the investigation of poliomyelitis. This led to the production by Salk of killed vaccine in 1953, and its use in a national campaign three years later. The live attenuated oral vaccine developed by Sabin between 1953 and 1956 was introduced in 1962. This has also been used in the control of such outbreaks as have occurred in recent years. By the end of 1965 20,721,248 in England and Wales had received a primary dose of Salk or Sabin vaccine. It was calculated that at that time 66% of three-year-old children, 65% of two-year-old, and 60% of one-year-old had been protected. In 1950 there were no fewer than 7,760 cases of poliomyelitis, with 755 deaths. The corresponding figures for 1965 were 90 and 19. Investigations carried out from 1962 to 1965 show that, while assurance cannot be given that vaccine never gives rise to cases of the disease, the chance is, at most, very small—in the nature of 1 in 4½ million doses. Also, it is improbable that vaccine strains cause disease among close contacts of those vaccinated. Taken at its worst, these seem small risks to run in order to contain one of the most alarming and handicapping infections of this century.

Reason for the Decline in Infections

Infectious diseases have shown a periodic ebb and flow. Smallpox, which became, as Macaulay described it, "the most terrible of all the ministers of death," was, so far as can be determined, slow in becoming a major infection. When first recognized in England four and a half centuries ago it does not seem to have given rise to a severe illness, but there may have been some confusion with measles. In 1837 to 1840, however, smallpox caused 41,644 deaths in England and Wales. This was one of the greatest epidemics, and marked the most devastating phase of the disease.

There is little evidence that diphtheria was common before the middle of the nineteenth century, although there were periodic outbreaks. Simon, when he first assumed the post of

Medical Officer to the Privy Council in 1858, wrote: "Diphtheria is a disease which, though it has been experienced in former times, is well-nigh unknown to the existing generation of British medical practitioners." Soon afterwards fresh infection was imported from Boulogne, and the disease became known as "Boulogne sore throat." Similarly, whooping-cough and tuberculosis have waxed and waned. Poliomyelitis has pursued a like course since the first outbreak was reported in this country at Workop in 1835. The decline of these infections since the introduction of immunization against them is shown in the Graph.

Graph showing decline of infections since introduction of immunizations.

The variations in virulence of some infections may be explained by a mutation of the causal organism or by the varying ratio of the causal types. For instance, the great influenza epidemics of 1847, 1889 (which caused 125,000 deaths), and 1919 (250,000 deaths) were presumably due to mutations, while it has been suggested that the severity of diphtheria depends on the proportion of gravis, mitis, and intermedius organisms. The change in recent years is shown in Table IV.

TABLE IV.—*Diphtheria Bacillus: Proportion of Types*

Year	Gravis (%)	Intermedius (%)	Mitis (%)	Atypical (%)
1933	75.6	4.3	20.1	—
McLeod (Leeds)	16.8	4.0	56.3	22.9
1955–65				
P.H.L.S.				

The proportions of the three types of poliomyelitis virus isolated by the Public Health Laboratory Service since 1956 have also altered sharply.

TABLE V.—*Poliomyelitis Virus Isolations (Cases and Excretors). England and Wales, 1956–65*

Year	No. of Isolations	Percentage of Total Isolations		
		Type 1	Type 2	Type 3
1956	849	86	7	7
1957	2,336	91	5	4
1958	1,223	94	1	5
1959	691	97	0	3
1960	352	62	1	37
1961	1,108	77	4	19
1962	596	56	19	25
1963	173	26	39	35
1964	216	30	37	33
1965	442	32	32	36

With this periodicity of the great infections, it is difficult to determine the part played by vaccination and immunization. Obviously other factors have been influential, such as better housing and smaller families reducing the risk of exposure (this has been particularly so in the case of tuberculosis, which Osler referred to as "a social disease with medical aspects"), welfare services giving rise to raised resistance, and improved medication reducing the risk of infection.

But, despite these influences, it is recognized that by decreasing the number of susceptibles "herd immunity" is built up. For in any disease spread by direct contact it is probable that once a certain balance between the immunes and susceptibles is reached, infection tends to die out. At present we know little of what this ratio is for the various infections and how long after it is achieved it is necessary to keep up prophylactic measures. It is well recognized, however, that there is no single critical level. The necessary proportion of immunes required to attain "herd immunity" will vary from area to area and from season to season, depending on the ease with which the causal organism may be transmitted and the number of susceptibles with whom the infected person comes into contact.

In support of the value of immunization it has been shown that, following the introduction of widespread immunization against diphtheria, the mortality from this disease, on a basis of the trend from 1866 to 1940, has been reduced to an extent quite different from whooping-cough and measles, and in a manner different from scarlet fever. The decline in scarlet-fever notifications in the past quarter-century has been sharp, but not so dramatic as with diphtheria. Further, the fatality rate in diphtheria has tended to rise during those years, while in scarlet fever it has fallen from 0.12 per 100 cases to 0.01. This recent decline in the virulence of scarlet fever is part of a long-term pattern, for after being a severe infection at the end of the eighteenth century it accounted for few deaths during the first four decades of the next. R. J. Graves of Dublin, one of those who first described exophthalmic goitre, maintained that the lower mortality was not due to better treatment but to a less virulent form of the disease. He was proved correct in 1840, when scarlet fever suddenly doubled its mortality in England and Wales. From then until 1880 it was the chief cause of death among the infectious diseases of childhood.

Above all there is the significant fact that, after the establishment of the national diphtheria immunization campaign, the responsible organism largely disappeared from the community. This has applied in more recent years, and to a lesser degree, in the case of poliomyelitis.

Prospects—Tomorrow's Horizon

With the increasing number of infections that can now be controlled by immunization and vaccination, the giving of the various antigens has become complicated and time-consuming. The perfection of the "dermojet gun" would expedite the immunization of large numbers, but the major handicap is the frequency of inoculations.

It is very desirable to develop combined vaccines of greater potency in which the constituent antigens are highly purified and concentrated, precisely quantified, and of minimal amounts, in a safe and effective adjuvant. This has proved difficult because of the need to get a balance between the various components and the varying responses—a good one to a second exposure to the same antigen and resultant less-effective reactions to the others. Again, better-based advice is needed as to when booster doses should be given. Antibody levels are imprecise guides, since they correlate only approximately with protection.

In all immunization programmes the problem is to reach the individual recipient. This is most easily achieved early in life, and the fewer injections needed the better. It may eventually

be possible to confer a sufficient degree of basal immunity by means of one dose of multiple vaccine and to reinforce protection against individual diseases as need arises. The investigation of the benefits, both in efficiency and in safety, from the sequential administration of killed and live antigens of the same type has only recently begun.

Generally, live attenuated vaccines give a better response than the killed variety; also they are less expensive, and easier to produce and administer. They are particularly advantageous for those infections in which there is a single or a few antigenic types, an extensive invasion of the host, and a lasting or life-long immunity. Smallpox and poliomyelitis are examples. Disadvantages are: side-reactions; poor keeping qualities, unless stored in the cold; and limited possibilities of incorporation in combined vaccines. Diseases in which the infection is more superficial, where there are numerous antigenic types, and in which immunity is not lasting appear to lend themselves best to the killed-vaccine approach. The human viral-respiratory-disease complex is the best example. Most virus vaccines are, however, likely to be evaluated by both methods.

The effect of giving an inactivated and a live vaccine simultaneously has been studied for a number of different antigens—for example, diphtheria-pertussis-tetanus vaccine with poliomyelitis live vaccine. Then the serological responses are equivalent to those when the antigens are given separately, and there are no more reactions. Similar results have been observed when oral poliomyelitis vaccine has been administered simultaneously with smallpox vaccine and with measles vaccine.

Measles

Since cases of measles became notifiable in this country in 1940 there has been a biennial rhythm-incidence, with, on the average, about 400,000 cases each year and as many as over three-quarters of a million in 1961. The illness has been generally mild, a trend which has increased over the past half-century, with the fatality rate only a tenth of what it was when notification was instituted. Nevertheless, epidemics of measles impose a substantial burden on patients, parents, and doctors, and complications are not negligible.

The Medical Research Council recently published the reports of a field trial, involving 37,000 children aged 10 months to 2 years, which showed that substantial protection had been achieved for at least six months by giving live vaccine alone or killed vaccine followed one month later by live. Reactions were relatively few and not severe. The duration of this protection has yet to be determined. It seems likely that before long measles vaccination, either alone or in combination with others, will become part of the national immunization programme.

Respiratory-Disease Complex

The viruses most responsible for respiratory illnesses are set out in Table VI.

TABLE VI.—*Respiratory Viruses of Man*

Myxovirus:
Influenza types A, B, C
Parainfluenza types 1, 2, 3, 4
Respiratory syncytial virus
Adenovirus:
More than 28 types
Picornovirus:
Enterovirus—
E.C.H.O.—at least 29 types
Coxsackie A—23 types
Coxsackie B—6 types
Poliiovirus—3 types
Rhinovirus—
At least 80 types; possibly many more

Since the isolation of the influenza virus in 1933 field trials carried out by the Medical Research Council have shown that various vaccines produce some transient protection. Unfor-

tunately the saline suspension causes some local and febrile reactions, particularly in children, and the water-in-oil emulsion gives rise to the very occasional abscess formation. The degree of protection conferred has been estimated variously as from 30 to 80%, the saline vaccine protecting for about a year and the emulsified for two years. It must be remembered that the natural disease gives immunity for only about four years. Again, when the influenza virus mutates sharply there is a complete failure of the necessary antibody formation by vaccines made from virus available before the mutation. A further difficulty is that, in these days of speedy travel, a new mutant might be widespread before a vaccine to protect against it could be produced and used on a large scale.

The claims recently made that the separation of virus haemagglutinin from the soluble antigen of the virus provides a product which is no longer pyrogenic and yet is antigenic holds out hope of advance and eventual incorporation in combined vaccines.

There is also prospect of progress in other parts of the respiratory-disease field. The parainfluenza agents cause severe disease of the lower respiratory tract in children, and their apparent antigenic stability makes possible the development of a vaccine. Similarly, a vaccine may be developed to control infection from the respiratory syncytial virus, which is probably the most important cause of respiratory-tract illness in children, including severe lower respiratory infection and mild upper respiratory disease. There is difficulty in determining which strains of adenoviruses are most responsible for human disease. Similarly with the picornavirus group, which includes the E.C.H.O. and Coxsackie viruses. A vaccine against the *Mycoplasma pneumoniae* (Eaton's agent) is, however, already on trial.

Much more beneficial than such vaccines would be one to combat the rhinoviruses, which are a principal cause of the common cold in adults and an important cause of upper and lower respiratory illnesses in children. Unfortunately this does not seem to be an imminent prospect, again because of the extreme complexity of the possible aetiology of such illnesses. If a limited number of immunological types are found to be of greater epidemiological importance than others, a worth-while immunoprophylactic might be possible. Otherwise, hope of controlling the common cold will depend on the development of other methods, such as chemoprophylaxis.

Vaccines against some other viral infections would be of advantage to protect certain groups. Examples of these are rubella and mumps, where the complications, rather than the disease itself, represent the major danger.

Rubella and Mumps

The production of a vaccine against rubella, which would reduce the risks of abortion, stillbirths, and congenital defects, arising from pregnant women contracting the infection in the first trimester of pregnancy, has proved difficult. Immunization of women of child-bearing age would remove the risk, with the general immunization of children as the ultimate aim, if the vaccine gave immunity of sufficiently long duration.

The use of mumps vaccine would probably be confined to specific groups of young adult males. Inactivated vaccines have been tested and found to give good protection, but of short duration. Recently, parenteral administration of attenuated virus has given encouraging results.

By contrast, there is no early prospect of vaccines to protect against varicella or viral hepatitis.

Further Possibilities

This does not end the prospects for virus vaccines, although the other developments may lie beyond tomorrow's horizon.

There is increasing evidence suggesting that some pre-natal, chronic, and degenerative diseases are of viral origin, and so may be controlled by vaccines. More intriguing still, study of animal cancers suggests that certain malignancies in man may also be caused by viruses. Thus it may be possible to prevent cancer by immunizing either the mother before the child is born or the infant shortly after birth. The science of immunology and mass immunization offers even greater promise of contributing to the health of mankind. Still, a virus-free world is not to be sought, since, no doubt, the challenge of coping with these invaders is much to human benefit. They present one of the stimulating dangers of being mortal.

Mass immunization has been so successful that we can now take heart in the knowledge that the control of acute infectious disease is no longer a sisyphian task. The price of success is not only energy but eternal vigilance, since not infrequently great epidemics of new infections have quickly and devastatingly swept this country. Moreover, Britain is no longer an epidemiological island, and in the less-developed countries, which account for more than two-thirds of the world's population, the acute infections are still the principal cause of death. Infectious diseases are foes which today are often underestimated, but even optimistic enthusiasts are compelled to face the realities that, Nature abhors a vacuum, and "what has been ; may be again."

There is a different type of danger ; of our ceasing to marvel at the transformation brought about even in our lifetime. If Gavin Milroy were to return to the scene after 80 years he would be astounded by what had been achieved and probably be irked at our quiet and unemotional acceptance of it. Upbraiding us, he might well echo the words of Lafeu in *All's Well That Ends Well*—"They say that miracles are past, and now we have our philosophical persons to make modern and familiar, things supernatural and causeless."

Summary

The State tried initially to control the spread of infectious disease by imposing isolation and quarantine in affected areas. Not long after the introduction of smallpox vaccination, at the end of the eighteenth century, this method of protection began to be officially sponsored. The experience from this and the later social, educational, and medical advances made possible the successful mass-immunization campaigns of the past quarter-century. The institution of a central organizing body—the Ministry of Health—and a source of scientific advice—the Medical Research Council—were other helpful factors.

Details of the mass-immunization campaigns are given and comment is made on the incidence of complications. The reasons for the decline of infectious disease, the prospects for making the present antigens more effective, and the developing of vaccines against other infections are discussed. The danger of a recrudescence of the infections, now in an attenuated form, or the evolution of new ones, is pointed out.