Immunization

CHILDHOOD AND TRAVEL HEALTH

GEORGE C. KASSIANOS
General Medical Practitioner

FOREWORD BY
PROFESSOR MIKE PRINGLE CBE

Blackwell
Science

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This fourth edition edition
is dedicated to my wife Karen
and our children Juliana,
Nicholas and Alexis
for their love and unfailing support.

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Other Editorial Offices:
Blackwell Wissenschafts-Verlag
GmbH
Kurfürstendamm 57
10707 Berlin, Germany

Blackwell Science KK
MG Kodenmacho Building
7–10 Kodenmacho Nihombashi
Chuo-ku, Tokyo 104, Japan

Iowa State University Press
A Blackwell Science Company
2121 S. State Avenue
Ames, Iowa 50014-8300, USA

First published 1990
Fourth edition 2001
Reprinted 2002 (twice), 2004

Set by BookEns Ltd, Royston, Herts
Printed and bound in Great Britain by
Marston Book Services Limited, Oxford

A catalogue record for this title
is available from the British Library

ISBN 0-632-05581-2

Library of Congress
Cataloguing-in-Publication Data

Kassianos, George C.
Immunization: childhood and
travel health
/G.C. Kassianos; foreword by Mike
Pringle.–4th ed.
p.; cm
Includes bibliographical references
and index.
ISBN 0-632-05581-2
1. Immunization of children–
Handbooks, manuals, etc. 2. Travel–
Health aspects-Handbooks, manuals etc.
3. Immunization–Handbooks, manuals,
etc. 4. Vaccination–Handbooks,
manuals, etc.
I. Title. [DNLM: 1. Immunization–
Child–Handbooks.
2. Communicable Disease Control–
Handbooks.
3. Disease Outbreaks–Handbooks.
4. Travel–Handbooks. 5. Vaccines–
Handbooks. QW 39 K19i 2000]

RJ20.K37 2000
614.4'7–dc21 00-051941

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Marston Book Services Ltd
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Foreword

It is a pleasure to write a foreword to the fourth edition of this remarkable book. In it George Kassianos offers even more advice and information and has updated the previous edition. Even more so than before, this is now the indispensable bible of the control of infectious disease, especially for primary healthcare.

When I was a medical student, the emphasis on infectious diseases was low. Tuberculosis was 'beaten'. Smallpox was being eradicated. Diphtheria, rheumatic fever and tetanus were becoming increasingly rare. For other bacterial diseases, antibiotics gave a sense of complacency. In a large part these successes were a result of improved living conditions and sanitation in the UK. However, they were also the result of an alliance between general practice and public health medicine in applying the new sciences of immunization, vaccination and disease control.

Those optimistic days are long past. While successes such as smallpox and diphtheria are still with us, the re-emergence of infections such as tuberculosis, the advent of antibiotic resistance, and the emergence of new types of meningitis and hepatitis and the spread of HIV have all dramatically raised the profile of infectious disease.

General practice has a key part to play. For prevention to be effective, immunizations and vaccines must be available and made acceptable. This means overcoming some understandable fears, counselling patients and parents, and ensuring that all are educated in the availability and benefits of such procedures. And this book is an essential part of that enterprise. Only with accurate and consistent messages can we persuade the public to join with us in the prevention of these major causes of morbidity and mortality.

But the contents of this book go much wider. Many infectious diseases are more common abroad and foreign travel advice is an important facet of modern general practice. Every practice needs to take this responsibility seriously and needs access to authoritative advice, as given here.

I recommend this valuable book to general practitioners, practice nurses and all those concerned with the reduction in infectious diseases in the UK.

Professor Mike Pringle, CBE
Council Chairman
Royal College of General Practitioners

Preface

It is now generally accepted that no other measure taken by man, apart from the provision of clean water, has ever saved more lives than immunization against infectious disease. Vaccines are among the safest and most successful public health tools available for preventing infectious diseases and their complications. Immunization is one of the areas at the forefront of family care in general practice. Effective and safe immunization, providing lasting immunity against infectious diseases, has made a major contribution to human welfare. Smallpox has been eradicated and, in countries with successful immunization programmes, we are witnessing virtual elimination of tetanus, diphtheria, poliomyelitis, pertussis, measles, mumps and rubella. The better the immunization programme, the greater the reduction in the morbidity and mortality of both bacterial and viral infectious diseases. *Failure to control infectious disease is primarily not because of vaccine failure but vaccination failure.*

Vaccines have provided us with the means of living without infectious disease. By using the vaccine to immunize, we aim to prevent infectious disease in the individual and the community. The ultimate goal of immunization is to eradicate infectious disease.

In 1974, when the Expanded Programme on Immunization (EPI) was launched by the WHO, less than 5% of the world's children were immunized against the six target diseases—diphtheria, tetanus, whooping cough, poliomyelitis, measles and tuberculosis—during their first years of life. By 1994, almost 80% of children under one, throughout the world, were immunized against these target diseases.

None the less, vaccine-preventable diseases kill 3 million children every year [Gwatkin D.R. & Guillot M. (1999) *The burden of disease among the global poor.* World Bank, Washington DC]. Millions more die from diseases, such as malaria and AIDS, that should be preventable by vaccines if they have been successfully developed. AIDS, tuberculosis, measles, malaria, diarrhoeal diseases such as dysentery and cholera, and acute respiratory infections such as pneumonia were responsible for 90% of all deaths due to infectious diseases around the world in 1998.

Unfortunately, existing vaccines are not reaching these millions of children because of failure in delivery systems, lack of resources, and high price of some newer vaccines. Moreover, new vaccines may not be developed because private companies cannot foresee a good return. The same has already happened with drugs. Of 1223 drugs developed between 1975 and 1997 only 11 were for tropical conditions [Trouiller P.T. & Olliaro P.I. (1999) Drug development output from 1975 to 1996: what proportions for tropical diseases? *Int. J. Infect. Dis.* 3, 61–3].

Infectious disease kills 17 million people worldwide every year. The WHO is aiming to stop neonatal tetanus and congenital rubella, as well as eliminate poliomyelitis from the world by the year 2000 (realistically this has been put back to year 2002 and after). It had a policy for universal hepatitis B immunization by the year 1997 but not all countries (including the UK) have taken up the challenge.

A new third world vaccination programme was launched in the year 2000, courtesy of Bill Gates' charitable foundation. The Global Fund for Children's Vaccines, which received $750 million from Gates, has made initial grants of $150 million to fund hepatitis B immunization programmes in 13 countries, including Cambodia, Mozambique and Rwanda. Around 30 million children do not have complete protection against vaccine-preventable diseases, and 3 million die every year.

Dramatic advances in molecular biology and the use of genetic engineering techniques are ensuring that over the next few years we will witness the introduction of a new generation of vaccines that will save the lives of millions of children every year. They include improved existing vaccines as well as vaccines for diseases for which no vaccines currently exist. We are going to see a range of combination vaccines as well as new delivery systems (oral, nasal).

In most circumstances immunization, particularly of young children, is an elective procedure. The vaccines used to immunize children against infectious diseases are among the safest medicines available to health professionals. It is, therefore, important to ascertain that no contraindications exist before any vaccination is carried out. *To deny a child vaccination can be to deny that child health.*

The aim of immunization is to protect the individual from suffering from serious infections, prevent local outbreaks, achieve high levels of immunization uptake thus creating 'herd immunity', prevent epidemics and eradicate infectious disease. Despite, or perhaps because of, the success of the UK immunization programme some parents have come to doubt the need to have their children immunized, particularly with the measles, mumps and rubella combined vaccine. This (in)action not only places their own children at risk, but also the population as a whole.

Part of the GP's and nurse's work is confidently to promote the benefits of immunization. This has to be done in the face of sporadic media scares and not only some hostility but also apathy among a minority of our patients.

Immunization is the most cost-effective public health intervention. The benefits of immunization are greatly under-recognized by a number of people. Vaccines have safely and effectively prevented more disease and death than any other medical intervention or treatment, including antibiotics. Improvement in living conditions, sanitation and the provision of clean water along with vaccines are contributing to the reduction in the loss of life all over the world.

In England and Wales we have seen a dramatic reduction of cases of infectious disease notified, thanks to the dedication of the healthcare workers, the Department of Health, the vaccine manufacturers and the availability of vaccines. Table 1 below shows the maximum number of cases notified in England and Wales in one year compared to the number notified in 1998. Soon we shall see the replacement of infectious disease by heart disease as the biggest killer in the world. Table 2 below shows the ten top causes of death in 1990 and those projected in year 2020 as estimated by the Harvard School of Public Health.

Table 1

	Number of cases reported	Maximum (year)	In 1998
Diphtheria	46,281	(1940)	23
Tetanus	24	(1976)	7
Pertussis	>100,000	(1975)	1,577
Poliomyelitis	4,000	(1955)	1
Haemoph.infl.b	1,259	(1989)	29
Measles	800,000	(1968)	3,728
Mumps	20,713	(1989)	1,587
Rubella	24,570	(1989)	3,208
Tuberculosis	50,000	(1950)	6,087

Members of the primary care team involved in immunization should speak with one voice and give similar and consistent advice and information to parents. This book is intended to help the GP, practice nurse and health visitor to present a united front in the fight for the total elimination of infectious diseases.

This fourth edition has been greatly revised and extended to include comprehensive advice on all immunizations performed in general practice. The previous style of starting with the contraindications to the vaccine and side-effects has been

Table 2

	1990	2020
1	Respiratory infections	Heart disease
2	Diarrhoeal disease	Severe depression
3	Complications of birth	Traffic accidents
4	Severe depression	Stroke
5	Heart disease	Chronic pulmonary disease
6	Stroke	Respiratory infections
7	Tuberculosis	Tuberculosis
8	Measles	War injuries
9	Traffic accidents	Diarrhoeal disease
10	Congenital anomalies	HIV/AIDS

retained, as this is the most commonly sought information in busy clinics.

I am very grateful to all those who have helped in the production of this book at Blackwell Science. Also to Ursula Shine and Jeannette Martin for their useful comments, and the Medical Information and Vaccines Departments of Aventis Pasteur MSD and SmithKline Beecham for their assistance. Special thanks to Usha Gungabissoon, information officer at the London Public Health Laboratory Service, Communicable Disease Surveillance Centre, Immunization Division.

Finally, I would welcome and value any reader feedback. Please contact me on authors@blacksci.co.uk.

George C. Kassianos

List of abbreviations

AAFB	Acid and alcohol-fast bacilli
ABPI	Association of British Pharmaceutical Industry
ACIP	Advisory Committee on Immunization Practices (USA)
Ads	Adsorbed
AIDS	Acquired immune deficiency syndrome
Anti-HBc	Antibody to hepatitis B core antigen
Anti-HBe	Antibody to hepatitis B e antigen
Anti-HBs	Antibody to hepatitis B surface antigen
APV	Acellular pertussis vaccine
BCG	Bacillus Calmette–Guérin vaccine
BMA	British Medical Association
BNF	British National Formulary
BP	British Pharmacopoeia
BW	Body weight
CABG	Coronary artery by-pass graft
CDC	Centers for Disease Control and Prevention (USA)
CDSC	Communicable Disease Surveillance Centre
CMO	Chief Medical Officer
COCP	Combined oral contraceptive pill
COPD	Chronic obstructive pulmonary disease
CRS	Congenital rubella syndrome
CSM	Committee on Safety of Medicines
d	Low-dose diphtheria vaccine for adults
DHF	Dengue haemorrhagic fever
DNA	Deoxyribonucleic acid
DoH	Department of Health
DOTS	Directly observed treatment short course
DT	Diphtheria/tetanus combined vaccine
DTaP	Diphtheria/tetanus/acellular pertussis combined vaccine
DTP, DTwP	Diphtheria/tetanus whole-cell pertussis combined vaccine
EEA	European Economic Area
eIPV	Enhanced potency inactivated polio myelitis vaccine
ELISA	Enzyme-linked immunosorbent assay
EPI	Expanded Programme on Immunization
ERVL	Enteric and Respiratory Virus Laboratory
ETEC	Enterotoxinogenic *Escherichia coli*
EU	European Union
FP10	General Practitioner's prescription
GMC	General Medical Council
GP	General Practitioner (family doctor)
h	Hour
HAV	Hepatitis A virus
HB	Hepatitis B
HBeAg	Hepatitis B e antigen
HBIG	Hepatitis B immunoglobulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDCV	Human diploid cells virus
HEV	Hepatitis E virus
Hib	*Haemophilus influenzae* b
HIV	Human immunodeficiency virus
HNIG	Human normal immunoglobulin
HVZIG	Human varicella-zoster immunoglobulin
ID	Intradermal
Ig	Immunoglobulin
IHPS	Infantile hypertrophic pyloric stenosis
IM	Intramuscular
IOS	Item of service
IPV	Inactivated poliomyelitis vaccine

IU	International unit
IV	Intravenous
kg	kilogram
L	litre
LMWH	Low molecular weight heparin
m	Months
Map	*Mycobacterium avium paratuberculosis*
MASTA	Medical Advisory Service for Travellers Abroad
MCA	Medicines Control Agency
MDR	Multiple drug resistance
MenC	Meningococcal C conjugate vaccine
min	Minutes
MMR	Measles/mumps/rubella combined vaccine
NOIDS	Notifications of Infectious Diseases
OMP	Outer membrane protein
ONS	Office for National Statistics
OP	Original pack
OPCS	Office of Population Censuses and Surveys
OPV	Oral poliomyelitis vaccine
OTC	Over the counter medicine
PA	Per annum
PCG	Primary Care Group
PCEC	Prurified chicken embryo cell
PCO	Primary Care Organisation
PCR	Polymerase chain reaction
PCT	Primary Care Trust
PHLS	Public Health Laboratory Services
POEC	Progesterone-only emergency contraception
POM	Prescription-only medicine
POP	Progesterone-only pill
PPA	Prescription Pricing Authority
RIBA	Recombinant immunoblot assay
RNA	Ribonucleic acid
RVA	Rabies vaccine adsorbed
s	seconds
SC	Subcutaneous
SFA	Statement of Fees and Allowances
SIDS	Sudden Infant Death Syndrome
SSPE	Subacute sclerosing panencephalitis
Td	Tetanus and low-dose diphtheria vaccine for adults and adolescents
UK	United Kingdom
UKCC	United Kingdom Central Council for Nursing, Midwifery and Health Visiting
US/USA	United States of America
VAPP	Vaccine-associated paralytic poliomyelitis
VZV	Varicella-zoster virus
WHO	World Health Organization

Part 1

Introduction to Immunization and Vaccines

Chapter 1

History of immunization

There is no doubt that immunizations have had a profound impact upon the incidence and prevalence of infectious diseases in the whole world. The vaccines have been used mainly in two ways: on an individual basis to protect specific persons at risk, and on a population basis to provide 'herd immunity', which is so important in combating infectious disease.

The origins of modern immunology are a matter of controversy. Some researches attribute fundamental notions about contagion and resistance to ancient Greek medicine, particularly to the Hippocratic notion of a constitution

The observation that recovery from smallpox prevented subsequent attacks of the disease was made in both ancient Greece and China. The concept of the protective effect of 'immunity' was established. About 1000 years ago the Chinese developed the technique of obtaining dried crusts from the pustules of smallpox patients, grinding them up and making them into powder, which was blown into the nose of the person being protected. Their aim was to induce immunity after a mild illness. This was perhaps the first attempt to induce immunity artificially by the process of immunization. This method of protection was not taken up to any significant extent outside the Far East at the time.

At the beginning of the eighteenth century it was becoming known that in the Middle East 'variolation' was being practiced. This involved the introduction of material from smallpox crusts into scarified areas of the skin, usually on the arm. The recipient would develop a mild form of the disease and then be afforded some protection against it. Variolation was introduced into Britain in 1721 by **Lady Mary Wortley Montagu** (1679–1762) who volunteered her daughter to be variolated. Lady Mary had observed the technique while she was in Constantinople, where her husband was the British ambassador to Turkey. During the same year this new technique was also introduced in America.

In the years 1720 and 1721, London was in the grip of a smallpox epidemic. Caroline, Princess of Wales, had seen one of her daughters nearly die from smallpox and sought to protect her other children by the new method introduced to England by Lady Montagu. Before going ahead with the treatment, Caroline requested that it be tried out on condemned prisoners. In 1721, an experiment was performed on six 'volunteers' from Newgate prison. Following variolation five developed mild smallpox but survived. The sixth had already had smallpox therefore no reaction was seen. They were duly pardoned. In order to test the technique, one of the five was later employed to work in an area with a high incidence of smallpox. When a local boy developed smallpox, she was ordered 'to lie every night in the same bed with this boy, and to attend him constantly from the first beginning of the distemper to the very end'. The experiment was thought to be successful as, in spite of this close contact, she did not develop smallpox.

In the eighteenth century in Britain, it was observed that dairymaids and cowmen did not seem to catch smallpox, although they were prone to develop cowpox. This observation led a Hampshire farmer, **Benjamin Jesty**, to believe he could protect his family against smallpox by 'inoculating' (the term was introduced around this time by the physician Emmanuel Timoni) them with cowpox material. Similar propositions were put forward by Jon Fauster, an apothecary, in 1765.

Twenty-two years later, on 14 May 1796, the first scientific attempt at immunization was made by **Edward Jenner** (1749–1823) in a hut in the garden of

Table 1.1 The development of human vaccination.

18th century	Smallpox 1796
19th century	Anthrax 1881, rabies 1885, diphtheria antitoxin 1891, plague 1897, cholera 1896, typhoid 1898
Early 20th century	BCG 1921, diphtheria toxoid 1923, pertussis 1926, tetanus 1927, yellow fever 1935, influenza 1945
Post World War II	Poliomyelitis (injectable 1955, oral 1962) measles (1960), mumps (1967), rubella (1962), pneumococcal, meningococcal, *Haemophilus influenzae* b, hepatitis A (1992), hepatitis B (1981)

his house in Berkeley, Gloucestershire. Jenner took some material from a cowpox pustule on the arm of Sarah Nelmes, a milkmaid, and scratched this into the arm of a young local boy named James Phipps. Young James developed a pustule and a mild fever following the experiment. He remained healthy when three months later Edward Jenner inoculated him with smallpox. This was the beginning of 'vaccination' (see Table 1.1 for the development of human vaccination).

Edward Jenner published his work in 1798 under the title *An inquiry into the causes and effects of the variolae vaccinae*. The word 'vaccinae' means 'of the cow'. The original meaning of the word 'vaccination' means 'protection against smallpox'. In the 50 years following Jenner's first inoculation, the number of deaths from smallpox in England fell from about 23 000 to 5000 a year. In 1853 smallpox vaccination of infants within 4 months of birth became compulsory in England. By 1980, smallpox had been eradicated from the world.

After Edward Jenner, the world had to wait for about a century for the next major advance which came from the work of **Louis Pasteur** (1822–1895), a brilliant chemist, physicist and microbiologist (he was not a medical practitioner). His earliest work on microbes, a term he coined from the Greek, was carried out when studying ways of preventing wine, beer and vinegar from spoiling. His discovery of the tiny creatures that spoiled these products, and his invention of a method of destroying them by heating the product, such as wine, to 60° C for a few moments, now known as 'pasteurization', has led to innumerable benefits for both industry and public health.

His aim was always prevention of disease. His words reflect exactly this: 'When meditating over a disease, I never think of finding a remedy for it, but instead a means of preventing it.' He worked tirelessly and with passion in his laboratory observing and experimenting. 'Nothing great has ever been accomplished without passion' was one of his comments. Speaking at his installation as professor and dean of the Faculty of Science, University of Lille, on 7 December 1854, he said: 'In the field of observation, chance only favours prepared minds.'

His work on the fatal illness of sheep called anthrax ('splenic fever') led to the discovery of the basic principles of immunity. Pasteur treated cultures of the anthrax bacillus in various ways until he found that microbes grown at a particular temperature range became harmless without losing their capability to provoke resistance in injected animals.

He demonstrated his new discovery in 1881 in front of the public and many scientists. Virulent cultures of the anthrax bacillus were injected into healthy sheep and an equal number of sheep previously inoculated with attenuated, harmless cultures. Within a few days all the unprotected sheep died and all the prepared sheep remained well. Pasteur had by now established the principal of immunity that attenuated cultures of an organism could afford protection against the disease caused by that organism. Jenner had obtained the same protection from smallpox by producing another illness, vaccinia or cowpox. Pasteur paid tribute to Jenner's work by calling his own method 'vaccination'.

Louis Pasteur's greatest achievement, however, was the discovery of a rabies vaccine. This followed earlier work he had undertaken on anthrax which had shown him, as mentioned above, that old, and therefore weakened, bacilli could be injected into

an animal, producing a mild form of the disease and giving lasting immunity. Partly paralysed by a stroke, Pasteur would work long hours in his laboratories with his assistants, **Pierre Roux** and **Charles Chamberland**, trying to identify the rabies organism, which he called virus from the Latin word for poison. All attempts to grow it *in vitro* failed. However, he succeeded in growing the rabies virus in the brain and spinal cord. He went on to discover a way of reducing its strength so that, when injected into an animal, it would give immunity without causing the disease.

On 6 July 1885, nine-year-old Joseph Meister from Alsace was bitten by a rabid dog. The family doctor believed he must risk vaccination or face a certain death. Pasteur injected young Joseph with the first of 14 daily doses of rabbit spinal cord suspensions containing progressively inactivated rabies virus. The vaccination was completely successful and Joseph Meister went on to become concierge at the Pasteur Institute in Paris. In 1940, he killed himself rather than admit the invading Nazis to the crypt where Pasteur is buried. Pasteur's method was so successful that it was rapidly adopted throughout the world.

Robert Koch (1843–1910) described the anthrax bacillus. In 1882 he isolated the tubercle bacillus and in 1883 the cholera bacillus. By 1884 he was able to define the four conditions that should be satisfied if the cause of a particular disease was to be ascribed to an organism:

- the organism must be present in every case of the disease;
- the organism must be isolated and grown as a pure culture;
- the culture should produce the disease when inoculated into a susceptible animal;
- the organism must be recovered from an infected animal and grown again as a pure culture.

Addressing a scientific meeting in Berlin, on 28 November 1902, Robert Koch advanced the idea of a healthy carrier of infection and applied it to the epidemiology of typhoid fever.

Two former assistants of Robert Koch first provided a treatment for the horrifying disease of diphtheria. **Emil von Behring** (1854–1917) and **Shibasaburo Kitasato** (1852–1931) were first to observe the formation of an antibody to a toxin—in this case, the toxin produced by the diphtheria bacillus. Von Behring showed that the body had a natural defence mechanism against toxins and that an animal injected with a sublethal dose of diphtheria bacilli would form antibodies, or antitoxins, which would enable it to fight off a later attack of the disease. On Christmas Eve 1891, a little Berlin girl suffering from diphtheria was treated with antitoxin prepared in a sheep and recovered. The concept of 'passive immunization' was now established. The work of von Behring and Kitasato led to the production of diphtheria (Ramon, 1923) and tetanus (Ramon and Zoeller, 1927) toxoids. The diphtheria antitoxin was first isolated by Paul Ehrlich (1854–1915).

In the meantime, the world saw the production of a plague vaccine by **Yersin** in 1897, typhoid vaccine by **Almroth Wright** in 1898, BCG (Bacillus Calmette–Guérin) vaccine by **Calmette** and **Guérin** in 1921, and typhus vaccine by **Weigl** in 1933.

A major landmark was the preparation of a highly successful yellow fever vaccine using chick embryo cells. It was introduced by **Theiler** in 1935. In 1941 experiments started with an influenza vaccine and in 1945 an influenza vaccine was developed by **Salk**. **John Huxham** (1692–1768), from Devon, was the first physician to use the term 'influenza' in 1750 in *An Essay on Fevers*.

The wall paintings of ancient Egypt showed children suffering from a mysterious illness, which wasted and crippled the limbs. Priests believed the disease was a mark of God's displeasure. In the nineteenth century poliomyelitis outbreaks became more common, with the worst one hitting the USA in 1916. Franklin D. Roosevelt lost the use of both legs when he contracted the disease in 1921 immediately after his defeat as a vice-presidential candidate. Roosevelt was later instrumental in promoting research, which made the USA the world leader in conquering the disease.

The three poliomyelitis viruses were first identified by an American team led by **John Enders** in 1949. The discovery that polio viruses could be grown in tissue culture enabled **Jonas Salk** of the University of Pittsburgh to produce an inactivated polio vaccine in 1954, and **Albert Sabin**—a Polish-born US microbiologist—an oral, attenuated form in 1957. John Enders and his coworkers, **John**

Franklin and **Thomas Weller**, were awarded the Nobel Prize for Medicine in 1954.

Soon thereafter, many viral vaccines were introduced. In 1954, Enders and **Peebles** isolated the virus causing measles from the blood and secretions of patients, which allowed Enders to develop the measles vaccine in 1960. In 1962, Weller developed the rubella vaccine. By 1967, the Jeryl Lynn strain of live attenuated mumps virus vaccine was introduced, **Maurice Hillman** having isolated the virus from specimens he obtained from his daughter Jeryl Lynn. In the 1970s, the work of **Krugman** paved the way for the successful development of a vaccine against hepatitis B, while the hepatitis A vaccine was developed in the early 1990s.

In the 1990s, we witnessed biotechnology open entirely new, highly scientific approaches to vaccine development. Examples are the rational and precise attenuation of bacteria and viruses to serve as live vaccines, the direct inoculation with plasmid DNA encoding protective antigens, and the microencapsulation of antigens to enhance immunogenicity and modulate the kinetics and type of immune response. The result is vastly improved vaccines (e.g. acellular pertussis vaccine) as well as vaccines, which are still being developed, against other diseases (e.g. malaria and Lyme disease).

The smallpox chapter of the history of immunization was closed when the World Health Organization (WHO) declared the disease officially eradicated in 1980. The eradication of measles in the Americas and the global eradication of poliomyelitis are the targets of WHO for the year 2000. Already, poliomyelitis has been eradicated in the Americas.

If a disease is eradicated, is then humanity safe? Well, it appears not. Take the case of smallpox. The WHO has now to rethink its policy to abandon and for ever destroy the last of the smallpox vaccine. One of the problems is monkeypox, a relative of smallpox and cowpox. The infection is spread from chimpanzees, other species of monkeys and squirrels, who are probably the most important reservoir of the virus. Monkeypox causes a syndrome clinically similar to smallpox and carries a high mortality—over 1 in 10 people who catch the disease in the rainforests of central and western Africa. Until recently, transmission was mainly from animal to human. During the 1996–97 outbreak of monkeypox in former Zaire, the main mode of transmission was person-to-person. Smallpox vaccination protects against monkeypox. Are we to reintroduce smallpox vaccination in any form or should we destroy the last remaining laboratory stocks of the smallpox virus?

It appears that clinical considerations are not enough. Smallpox virus is a most dangerous organism that might be used by bioterrorists. The international black market trade in weapons of mass destruction is probably the only means of acquiring the deadly virus. Officially, the smallpox virus now exists in two government-run laboratories in the USA and the Russian Federation; at the Centre for Disease Control and Prevention in Alabama, and at the Russian State Centre for Research on Virology and Biotechnology in Siberia. Many scientists believe that samples are also being held in secret elsewhere.

The last recorded cases of smallpox were in Somalia in 1978, and also in Birmingham, UK, during the same year, when the virus escaped from a laboratory, killing one person and driving the scientist in charge of the laboratory to suicide. Smallpox samples in laboratories around the world were progressively destroyed throughout the 1980s. It is possible that not all laboratories complied fully. The possible use of smallpox virus as a weapon by terrorists has stimulated growing international concern and led to a review by WHO of the global availability of smallpox vaccine. This review (1999) found approximately 60 million doses worldwide. It is estimated that the USA alone will need to stockpile at least 40 million doses of the vaccine for emergency use, including in case of a terrorist release of smallpox virus.

In 1996, the World Health Assembly agreed the destruction, by 30 June 1999, of the two known stocks in the USA and the Russian Federation mentioned above. The new decision is 'the temporary retention, up to but not later than 2002, of the existing stocks of variola virus'. The final elimination of all variola virus remains the goal of WHO.

Furthermore, an international group of scien-

tific and public health experts who met at WHO, Geneva, Switzerland, in December 1999, has recommended that more research should be undertaken on the smallpox virus before the end of 2002 when the two remaining collections of the virus would have been destroyed. The experts said that the DNA of the virus should be sequenced more completely, tests should be devised to detect human smallpox infection, and drugs should be developed to treat smallpox infections.

Bioterrorism fears have prompted the USA to set up a study on the safety and effectiveness of Dryvax. This smallpox vaccine is no longer produced but part of the limited supply still available in the USA will be used for a study in which 60 people will be given a full, one-tenth or one-hundredth dose of the vaccine. Information can be obtained from the Saint Louis University website: www.slu.edu. Readers can obtain further information on the subject of smallpox via the internet on the WHO home page: www.who.int.

About 200 million children are born worldwide each year, of whom 140 million are born in less developed countries. Despite all the efforts of the world community, 2 million children still die every year from immunization-preventable diseases. Yet, immunization coverage is levelling off in many countries and falling in others. The world community is responding; an International Vaccine Institute has opened in Seoul, Korea (www.ivi.org): new or expanded cooperative research efforts include the Multilateral Initiative on Malaria (http://www. malaria.org/MIM.html), and the international AIDS Vaccine Initiative (http://www.iavi.org).

Fighting infectious diseases in the developing world is a priority for all nations if we are to control and eventually eliminate them. An important element in this is the Millennium Vaccine Initiative (MVI) announced in February 2000. UNICEF, WHO and various other organizations are creating a new Global Alliance for Vaccines and Immunization (GAVI) http://www.who.int/gpr-aboutus/gavi. It aims to help lower the toll of infectious diseases, which accounts for a quarter of all deaths worldwide. In addition to the extra $150 million in the US budget for the year 2001 to fight human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) and other infectious diseases, the US President proposed a new tax credit to speed development of new vaccines. The Bill and Melinda Gates Foundation has pledged $750 million over 5 years for the GAVI (http://www.gatesfoundation.org). Merck has pledged 5 million doses of its hepatitis B vaccine over 5 years. American Home Products have pledged 10 million doses of its *Haemophilus influenzae* b vaccine. SmithKline Beecham announced it would undertake paediatric trials of its malaria vaccine in Africa and renewed a pledge made in 1998 to work with WHO to donate 5 billion doses of albendazole over the next 20 years to eradicate lymphatic filariasis; Aventis Pharma has pledged 50 million doses of its polio vaccine for 'war-torn nations of Africa'.

The twentieth century witnessed a revolution in immunology and saw the introduction of vaccines that led to the reduction or elimination of 21 infectious diseases. Can the twenty-first century do better? It should!

Chapter 2

Timescale of vaccine introduction in the UK

1938	Smallpox vaccination—the only routine immunization
	Tetanus toxoid—for military personnel
1940	Diphtheria toxoid (in some cities it began in 1937)
1946	Trials of pertussis vaccine
1948	Compulsory smallpox vaccination ended
1949	BCG vaccination for health service staff and contacts of tuberculous patients
1953	BCG vaccination in general use
	Pertussis vaccine (usually combined with diphtheria)
1956–61	Tetanus toxoid routinely for children, initially in some areas as monovalent and nationally in 1961 as diphtheria/tetanus/pertussis (DTP)
1961	DTP combined vaccine
1961	Oral polio vaccine (Sabin)
1967	Influenza vaccine
1968	Measles vaccine
1970	Rubella vaccine
1971	Smallpox vaccination discontinued
1975	Human diploid cell rabies vaccine
1979	Pneumococcal (14-valent) vaccine
1982	Hepatitis B plasma-derived vaccine
1987	Hepatitis B recombinant yeast vaccine
1988	Measles/mumps/rubella (MMR) combined vaccine
1989	Meningococcal A and C polysaccharide vaccine
1992	Hepatitis A vaccine
	Haemophilus influenzae b vaccine
	Pneumococcal (23-valent) vaccine
	Oral and Vi antigen typhoid vaccines
1994	Tetanus and low-dose diphtheria vaccine for adults and adolescents (Td)
	Acellular monovalent pertussis vaccine
	Measles/rubella combined vaccine
1997	Combined hepatitis A and B vaccine
	Combined DTP-Hib vaccine
1999	Combined hepatitis A and typhoid vaccine
	Meningococcal C conjugate vaccine
	Diphtheria/tetanus/acellular pertussis vaccine
	Diphtheria/tetanus/acellular pertussis–inactivated polio vaccine
	Diphtheria/tetanus/acellular pertussis–haemophilus influenza b vaccine
2000	Acellular monovalant pertussis vaccine no longer available

Chapter 3

Immunology, immunization and vaccine development

In the Golden Age of immunology and bacteriology (1870–1910) it was discovered that particular microbes were responsible for specific diseases. This eventually led to the development of vaccines, which have controlled several major infectious diseases. Vaccines are probably biomedical science's greatest triumph.

Immunization is the induction of artificial immunity through the administration of a vaccine or immunoglobulin. The term is commonly used interchangeably with *vaccination* (protection against smallpox)—it refers to the process of immunization. Vaccination is the administration of one or more doses of vaccine. As a result of this, and if vaccination is successful, the vaccinee is immunized (acquires immunity) against a specific infectious disease, thus becoming immune to that disease.

Immunity is the development of a relative resistance to an infection. This can be acquired from the mother *in utero* and during breast-feeding, actively from a pathogen able to mount an immunological response (infection, vaccine), or passively through the administration of ready-made anti-bodies in the form of immunoglobulins. Following natural infection, immunity may be lifelong.

Immune response is the recognition of antigens associated with pathogenic organisms by the body's defence system and operates in the form of a collection of tissues, cells and molecules. This response can be *antibody-mediated* (directed against extracellular pathogens) or *cell-mediated* (against intracellular pathogens) and is specific. A *memory* developed from previous experiences of foreign material ensures that a future challenge provokes a faster and more vigorous response.

Passive immunity

Immunity that can be induced by giving preformed antibodies is referred to as passive immunity. This is short-term immunity and can be achieved by giving nonspecific human normal immunoglobulin, collected from pooled human blood donations that contain antibodies to infectious agents prevalent in the community (e.g. for hepatitis A, measles), or specific immunoglobulin, formed from high-titre sera from humans or animals recently vaccinated or who have had the infection (e.g. varicella zoster, hepatitis B, tetanus, rabies). A neonate can acquire passive immunity from the mother's antibodies crossing the placental barrier and/or in breast milk.

Although passive immunization gives rapid protection within 24–48 h of intramuscular administration of the immunoglobulin, it does not last long, up to 6 months depending on dose given.

Active immunity

Active immunity is created by giving an antigen as a vaccine, containing organisms that have been:

- killed (e.g. heat-killed whole-cell typhoid vaccine; no longer available in the UK);
- attenuated—live organism with low virulence (e.g. measles, mumps, rubella, oral polio, BCG);
- inactivated bacterial toxins (e.g. with formaldehyde as in the case of diphtheria and tetanus);
- inactivated organisms (e.g. parenteral polio vaccine, hepatitis A);
- inactivated selected antigens of the organisms (e.g. pneumococcal capsular polysaccharide, influenza);
- genetically engineered (as in the case of hepatitis B vaccine).

Vaccines produce humoral immunity (i.e. most bacterial vaccines) or cell-mediated immunity (i.e.

the live virus vaccines, including the live bacterial BCG vaccine).

Humoral immunity

Activation of B-lymphocytes produced by the bone marrow (so known from the 'bursa of Fabricius', a gut-associated lymphoid organ where chicken lymphocytes were found to require a period of differentiation) by an antigen results in the production of millions of *antibodies*. Their task is to bind to the antigen and neutralize it.

Each B-cell is programmed to encode a surface receptor specific to a particular antigen (the surface antigen of a microorganism, a toxin, etc.). Once B-cells have recognized their specific antigens, they multiply and differentiate into plasma cells capable of producing large amounts of the receptor molecule in a soluble form—the antibody. Antibodies are large glycoproteins (*immunoglobulins, Ig*) and can be found in the blood and tissue fluids. They are virtually identical to the original receptor molecule, therefore they bind to the antigen that initially activated the B-cell.

Early in the humoral immune response IgM antibody is produced (primary response—disappears after a few months), but later large amounts of IgG mature antibodies (longer lasting—secondary response) are released in the blood and body tissues. When IgA antibodies are formed, they are secreted across mucosal surfaces in order to provide protection in the respiratory tract or the gut. An example here is the oral vaccines, which can produce local gut immunity as well as antibodies in the general circulation. These responses are important first-line defences against future infection.

Simultaneously, large numbers of *memory cells* are produced. These are antigen-specific B-cells. Further antigen exposure provokes a fast and vigorous antibody response.

Neutrophils are white cells that migrate to the site of invasion and destroy microorganisms by *phagocytosis* (from the Greek *phago* to ingest and *cytos* the cell). *Macrophages* are mononuclear white cells, able to ingest bacteria that have been coated with complement component (one of the main mediators of the inflammatory response) or antibody.

Following completion of the immunization course, the IgG levels will remain high for some time. When the level falls, a further dose of the vaccine (a booster) will reinforce immunity by increasing the IgG level again. This is not the case after polysaccharide vaccines when a booster dose does not increase the response (does not raise the antibody titre) but just sustains it.

Cell-mediated immunity

The cell-mediated immune response is a system of lymphocyte-mediated immunity that does not depend on major production of antibody. It relies more on a system of antigen recognition and cytokine production among macrophages and T-cells.

T-cells are lymphocytes that require a period of differentiation in the thymus gland and this gives rise to the designation *T-lymphocytes*. Once activated, T-cells produce cytotoxic cells, which destroy in-fected cells, and cytokinins, which prevent microorganisms from replicating within cells.

There are two major types of T-cells: CD4 (T-helper cells) and CD8 (T-suppressor or cytotoxic cells). CD4 T-cells stimulate B-cells to produce antibodies and also produce cytokinins—soluble mediators of immunity. Cytokinins, in turn, activate macrophages to destroy intracellular pathogens.

CD4 lymphocytes can be categorized according to the cytokinins they produce. These subsets have distinct functional characteristics: T-helper 1 (Th1) cells make γ-interferon (activates macrophages and T-cytotoxic cells, has a major role in eradication of viruses) and are associated with cell-mediated immunity, while T-helper 2 (Th2) cells make interleukin-4 and -5, and help B-cells produce antibody.

Within the past five years comparable populations of CD8 lymphocytes have been identified. Their task is to destroy host cells which have become infected by viruses or other intracellular pathogens—this action is called cytotoxicity. T-cells generate their effects by releasing soluble proteins (cytokinins), or by direct cell–cell interactions. The T-cytotoxic 1 (Tc1) lymphocytes make γ-interferon, an efficient killer cell that also inhibits Th2 cells. T-cytotoxic 2 (Tc2) lymphocytes make interleukin-4 and -5, less efficient killer cells that inhibit Th1 cells.

Immunological memory

Immunological memory is the situation where the vaccine-induced immunological 'memory' sustains immunity in the absence of detectable, or the presence of low, antibody. A rapid response in the antibody titres after a booster dose of vaccine is indicative of immunological 'memory'. An example is the case of hepatitis B when the anti-HBs level is below 10 mIU/mL or not detectable. Some lymphocytes become 'memory' cells with capacity for clonal expansion, differentiation and production of antibody upon subsequent stimulation by hepatitis B surface antigen (HBsAg). The principle of immunological memory could apply to other immunizations such as tetanus, hepatitis A, and probably diphtheria and measles.

Acquired immunity

A mother passes her antibodies to infectious diseases (passive immunity), which she has acquired through infection or vaccination, to her newborn child via the placenta and breast milk. Once these maternal antibodies wane, the child becomes susceptible. The child can acquire (active) immunity by vaccination or infection.

For infectious diseases to which a newborn child will be at immediate risk (such as tuberculosis in prevalent areas or hepatitis B where the mother giving birth is infected), the vaccines are given at birth. For a short period after birth (2 or 3 months) infants have some passive immunity from antibodies passed on to them *in utero* for diseases such as diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* and meningococcal infection. This depends greatly on whether the mother is immune, and whether this immunity is by natural infection or immunization (and how recent vaccination was). Breast milk does not give protection against infections such as diphtheria, tetanus and pertussis.

In deciding when to commence immunizations one has to balance the time an infant will obtain good immunity from immunization against the risk of disease. Pertussis kills very young infants and most of the deaths are seen in those under 2 months old. Pertussis vaccine will take from birth, but maternal antibodies to tetanus persist in the child for several weeks and would 'mop up' the tetanus vaccine. This is why in the UK we commence childhood immunizations at the age of 2 months. The WHO recommends starting the primary course at 6 weeks, so it is safe to start early—for example, if the family is flying abroad. With regard to measles, any persisting passively acquired (*in utero* and breast milk) maternal antibodies can interfere with the ability of the child to respond to the vaccine, if given during the first year of life, hence the postponement of vaccination until the child is over 1 year of age.

The killed organism vaccines are generally given more than once in order to produce sustained immunity, while live vaccines are generally given only once.

Vaccine production

Vaccines are produced in different ways depending on the microorganism and whether viral or bacterial, live or inactivated.

Viruses are parasites that can only grow in living cells, therefore they have to be produced in live cell cultures. The viruses for some viral vaccines are grown in hens' eggs. The process starts with a small 'laboratory' culture that is progressively scaled up to larger and larger culture vessels. This process takes time and cannot be accelerated. Bacterial vaccines are produced in a similar way, with production being scaled up over a period.

Once the microorganism is grown, it is inactivated or split into smaller units. The active component of the vaccine is then highly purified and blended with the other constituents of the vaccine to produce 'the bulk'. This process takes 4–9 months.

The next step is the testing of the bulk in order to ensure that it contains the correct organism; it has not changed during the growth period; it is free of contamination; and it does contain the correct ingredients in the correct amounts. Testing can take a further 1–3 months. If the vaccine is combined (e.g. MMR or DTP), the bulk of all constituents has to be further blended and tested. Once the manufacturer is satisfied that the bulk vaccine meets the stringent criteria set by the product licence, samples of the bulk are released to

the authorities so that they can perform their tests. The whole process can take a year or more.

Once quality control is secured, the bulks are then used to fill in the appropriate containers (syringes, ampoules, vials). Before a vaccine is released, further tests are carried out to ensure that it conforms to the product licence. This process takes a further 4–10 weeks. The next step is further testing of the bulk and the finished product by one of several European Official Medicines Control Agencies—for vaccines to be used in Europe. This takes up about 2 months. Once satisfied of the quality of the product, the manufacturer proceeds to packing and distribution. By now, and provided no delays were encountered, an average of 20 months have elapsed since the start of production of the vaccine.

Planning vaccine production is essential for the manufacturer as well as the immunization authority of a country. Despite every effort by the manufacturer to produce enough vaccines, we frequently witness shortages of vaccine worldwide. Among the reasons for these shortages are the following:

- epidemics, and emergency programmes;
- new national immunization campaigns;
- new recommendations being adopted;
- steadily increasing vaccine demand;
- manufacturing capacity limits and manufacturing problems.

Conjugate vaccine technology

A good example of conjugate vaccine technology are the *Haemophilus influenzae* b and meningococcal C vaccines as well as others developed since the early 1970s. Such vaccines contained purified capsular polysaccharides (long-chain sugars forming 'bacterial coats' covering the surface). While effective in adults, they were generally ineffective in children under 18 months of age—the most vulnerable group. In this age group polysaccharide vaccines are unable to induce memory in T-lymphocytes and therefore give them only brief protection.

The aim was to produce vaccines that would be effective in preventing disease in children of all ages as well as adults. This was achieved by new conjugate vaccine technology which permanently links (conjugates) purified polysaccharides to purified proteins (carrier molecules) rendering them immunogenic, thereby improving the vaccine immunogenicity, even in children under the age of 1 year. A nontoxic derivative of diphtheria toxin, group B meningococcal outer membrane protein, diphtheria and tetanus toxoids, among others, have been used to conjugate capsular polysaccharides.

Adjuvant

In order to enhance the antibody response to the antigen and prolong the stimulatory effect, some inactivated vaccines contain adjuvants. These are most commonly derived from minerals, oily materials or derivatives of certain microorganisms. Examples are aluminium phosphate and aluminium hydroxide.

Preservatives, stabilizers, antibiotics

In order to prevent bacterial growth or to stabilize the antigen, trace amounts of chemicals (e.g. mercurials such as thiomersal, antibiotics such as streptomycin, neomycin or penicillin) are frequently needed. Allergic reactions can occur if the vaccinee is allergic to these additives. The vaccine is contraindicated if the person to be vaccinated is expected to exhibit an anaphylactic reaction as a result of contact with these substances.

Thiomersal is 49.6% mercury by weight, and metabolizes to ethylmercury and thiosalicylate. It has been used for over 60 years as an antibacterial preservative in vaccines, and is particularly useful in maintaining bacteriological safety of opened multidose vials. At doses much higher than those used in vaccines, this preservative has been reported to cause neurotoxicity and nephrotoxicity. However, the precise nature of toxicity from low concentrations of exposure to thiomersal remains uncertain.

There are no data on and no evidence of the toxicity of ethylmercury at such low levels as in vaccines, but new guidelines make the (as yet unproven) assumption that it has the same toxicity as methylmercury. The WHO supports the 1999 statement from the American Academy of Paediatrics that it is to be phased out over the next few years, although it

is accepted that there is no evidence that thiomersal has caused any harm in the amount contained in vaccines (< 0.05 mg). The USA Public Health Services, the American Academy of Paediatrics and vaccine manufacturers have agreed that thiomersal-containing vaccines should be replaced to avoid any theoretical risk and unnecessary exposure to mercury. This action is not urgent, but will take place as expeditiously as possible.

The UK childhood immunization schedule contains a much smaller number of routine vaccinations than the USA schedule and it is therefore unlikely that the use of thiomersal is a significant problem there.

The WHO has stressed the importance of continuing to use existing children's vaccines in the light of moves to phase out the use of thiomersal. It notes that the risk to unvaccinated children of death and complications from vaccine-preventable diseases is 'real and enormous', while the risk from side-effects of thiomersal is 'theoretical', uncertain and, at most, extremely small. Thiomersal has been in vaccines for many years with no adverse effects being seen. Furthermore, the WHO states that although there are other chemicals which could be used as preservatives, none is as effective as thiomersal. Also, if a new preservative is used in a vaccine, or thiomersal is omitted, the vaccine will have to undergo regulatory approval as a new product, which could be a lengthy process. Already, hepatitis B vaccines are available in the USA that do not contain thiomersal.

Serum albumin

Concern has been raised over the risk of transmission of bovine spongiform encephalopathy (BSE) and Creutzfeld–Jakob disease (CJD) from vaccines resulting from the production process and final constituents of vaccine. This risk remains hypothetical. None the less, no vaccine used in the UK childhood immunization programme since 1994 has contained UK human albumin. All UK vaccines using bovine albumin have been sourced from outside the UK since well before 1994. The rabies vaccine currently issued by the Public Health Laboratory Service (PHLS) is the only vaccine that does contain UK human albumin. Until further advice is received from the Committee on Safety of Medicines (CSM) it will be issued for pre- and postexposure prophylaxis where there is clear indication for the use of this vaccine.

Testing the vaccine

In the UK no vaccine is licensed until it has been tested for safety, efficacy and acceptability. Before obtaining a licence a vaccine has to undergo testing in three phases.

Phase I

The safety and overall tolerability of the vaccine is tested on a small number of human healthy adult volunteers.

Phase II

Here it must be proved that the vaccine is safe and effective in producing antibodies capable of preventing the disease among the population. The dose, age ranges and vaccination schedules are also worked out.

Phase III

The vaccine is now tried on the population it is meant to protect, e.g. the Hib vaccine in the under 4- and especially under 1-year-olds.

Beyond phase III is continued *postmarketing surveillance* of the vaccine. The Post Licensing Division of the MCA has a responsibility for monitoring the safety of vaccines.

'Named-patient' basis

Some vaccines or immunoglobulins that have not been submitted to the UK authorities for licensing or that have not obtained a licence, can be made available on a 'named-patient' basis. In legal terms, supply of a product under this provision renders ultimate liability for its use with the prescribing clinician.

'Black triangle'

A new vaccine or immunoglobulin may carry the 'black triangle' in the British National Formulary (BNF). In this case we are asked to report *all* suspected reactions, however minor, that could conceivably be attributed to the preparation bearing the black triangle. Reports should be made despite uncertainty about a causal relationship, irrespective of whether the reaction is well recognized, and even if other drugs have been given concurrently.

Definition of terms used in clinical trials of vaccines

To define terms used in clinical trials of vaccines, let us take as an example the hepatitis B recombinant vaccine.

Immunogenicity (*immunogenic efficacy*) refers to the titre of anti-HBs antibody produced in the person receiving the vaccine. It can be assessed by the sero-conversion rate (the percentage of individuals who seroconvert—see below) and the geometric mean titre (GMT) of anti-HBs generated by the vaccines after primary vaccination.

Seroconversion is the creation by vaccination of an anti-HBs titre that is equal or greater than 1 mIU/mL. It means that antibodies have been developed and detected by current laboratory techniques in a person whose blood did not previously contain these antibodies, following the introduction of an antigen into the body. Before seroconversion the subject is said to be *seronegative* while after seroconversion the subject is *seropositive*.

Seroprotection, in the case of hepatitis B vaccine, is where the vaccine produced an anti-HBs titre equal or greater than 10 mIU/mL (minimum required to protect).

Protective efficacy is the prevention by the administration of hepatitis B vaccination of future acute symptomatic hepatitis B and hepatitis B virus (HBV) carriage.

Combined vaccines

If the British child received the vaccines in single antigens, by the time the child was 2 years of age, it would have received three oral doses and 18 injections. At the moment, it receives three oral doses and seven injections thanks to combination vaccines. Future vaccines will predominantly be combined vaccines. This involves combining a number of antigens in one syringe in order to minimize the number of injections required. The US Food and Drug Administration (FDA) requires that a combination vaccine not be inferior in 'purity, potency, immunogenicity, or efficacy' to each agent given separately.

Paediatric vaccines are being developed which will eventually combine the following antigens into one vaccine: diphtheria, tetanus, whole-cell or acellular pertussis, inactivated polio, *Haemophilus influenzae* type b, meningococcal A, B, C, hepatitis B, hepatitis A and yellow fever. Already a combination vaccine has been developed that incorporates DTaP–IPV–HBV–Hib (Infanrix HeXa, Smith Kline Beecham; HEXAVAC, Aventis Pasteur).

In the UK, vaccines that combine various antigens have been licensed:

- diphtheria/tetanus combined vaccine (DT);
- tetanus and low-dose diphtheria vaccine for adults and adolescents (Td);
- diphtheria/tetanus/whole-cell pertussis combined vaccine (DTwP);
- DTwP and Hib;
- DTaP (Infanrix);
- DTaP–IPV (Tetravac)
- MMR;
- meningococcal A + C;
- hepatitis A + B (Twinrix);
- hepatitis A and typhoid (Hepatyrix).

The benefits of combined paediatric vaccines are:

- fewer injections, thus less discomfort for the children;
- less stress for the accompanying parents;
- improved acceptance of existing and newly recommended vaccines;
- increased compliance;
- a more effective immunization programme;
- lower drop-out rates;
- greater convenience for doctor/nurse;
- lower administration cost;
- simpler logistics (transport, storage, records);

- less time to prepare and administer the vaccines;
- lower overall cost of immunization programmes;
- fewer visits to the doctor—fewer inoculations, contacts;
- simpler to protect against more than one infectious disease;
- real chance to eradicate polio if the inactivated form in the combined vaccine is used universally (we still see, rarely, vaccine-associated paralysis with the live oral polio vaccine);
- simplification of immunization schedule;
- enabling of reluctant countries to accept a particular vaccine, as may happen with the UK and childhood hepatitis B immunization.

The future vaccines

The success of existing vaccines depends on their ability to induce production of antibodies, which are the principal agents of immune protection against most viruses and bacteria. There are, however, exceptions, including intracellular organisms such as *Mycobacterium tuberculosis*, the malaria parasite, *Leishmania* and possibly the human immunodeficiency virus (HIV), in which protection depends more on the cell-mediated immunity than on induction of antibodies (humoral immunity). With the exception of vaccines prepared from live attenuated organisms, the others do not bring about cellular immunity. For these reasons, a new approach to vaccination, which involves the injection of a piece of DNA that contains the gene for the antigen, has been developed.

It is my belief that DNA vaccines will have a very important role in the future. We are witnessing an explosion of DNA vaccine research and some exciting results are coming out of many laboratories.

The new DNA vaccines (polynucleotide expression vectors) represent a new generation of vaccines to come. By encoding proteins derived from various pathogens, researchers have demonstrated that this can be an effective way of generating both humoral and cellular immune responses following intramuscular injection (see Fig. 3.1). In a DNA vaccine, the gene for the antigen is cloned into a bacterial plasmid that is engineered to augment the expression of the inserted gene in the mammalian cells. After being injected into the muscle, the plasmid enters a host cell, where it remains in the nucleus as an episome (from Greek meaning additional body); it is not integrated into the cell's DNA. Using the host cell's metabolic machinery, the plasmid DNA in the episome directs the synthesis of the antigen it encodes.

DNA vaccines are generally:

- fundamentally different from other vaccines;
- easier to produce and purify;
- easy to modify;
- relatively inexpensive;
- may not require cold chain;
- are highly immunogenic, especially for CD8 T-lymphocyte cells.

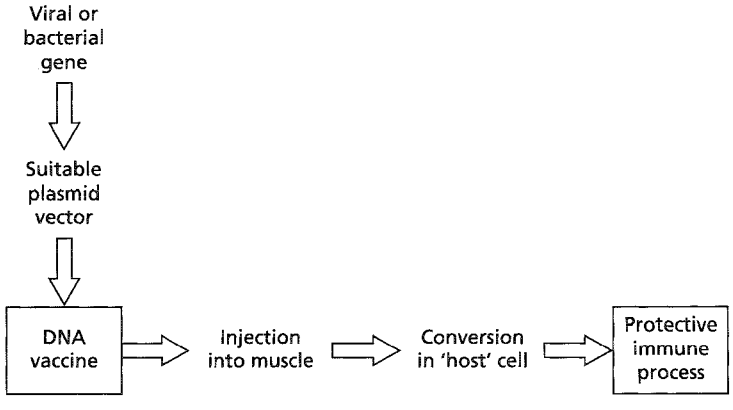

Fig. 3.1 The DNA vaccine.

Experimental work with DNA influenza vaccine has demonstrated three very important advantages over existing vaccines:

1 it produces a higher antibody level in monkeys than the inactivated whole-cell or split virion vaccines;
2 it stimulates strongly the cell-mediated immune response (it evokes a strong cytotoxic T-cell response to viral nucleoprotein);
3 it demonstrates the ability to protect from antigenic shifting of the influenza strains (one of the reasons for the yearly vaccination). Mice immunized with DNA encoding the nucleoprotein on an H1N1 1934 strain of influenza were greatly protected from death and morbidity (90% of them survived as opposed to 20% of the controls) following challenge with an H3N2 1968 strain of influenza virus.

Work is now continuing to apply this DNA technology to tuberculosis, genital herpes, influenza, HIV, hepatitis B and C, rabies, malaria, papillomavirus, Japanese b encephalitis, dengue and carcinogen antigens.

Remaining issues for the scientists are the full safety profile of these DNA vaccines, induction of anti-DNA antibodies, autoimmunity, induction of tolerance, their human efficacy and stability.

Vaccines under development

Some of the vaccines currently under development are:

- asthma/pneumonia vaccines (respiratory syncytial virus, house dust mite, cat antigens);
- prostate cancer vaccine;
- gastric cancer (*Helicobacter pylori*);
- cervical cancer (human papillomavirus);
- breast cancer;
- metastatic renal carcinoma—immunotherapy;
- leukaemia;
- melanoma;
- hepatocarcinoma (hepatitis C, complementing existing hepatitis B vaccine);
- malaria;
- dengue fever
- schistosomiasis;
- tuberculosis (adults);
- AIDS;
- diarrhoeal diseases (rotavirus, cholera, *Shigella*, enterotoxigenic *Escherichia coli*);
- meningitis and otitis media (*Streptoccocus pneumoniae, Neisseria meningitidis* group B);
- autoimmune diseases (insulin-dependent diabetes mellitus, multiple sclerosis);
- Alzheimer's disease;
- Angiotensin vaccine for hypertension.

Already vaccines for Lyme disease and rotavirus infections exist, and clinical trials are in their final stages for dengue fever vaccines. Phase I and III trials have commenced in the UK with different human papillomavirus vaccines; already trials are being completed in the USA. One early application this vaccine may have in the UK is its use in women who are at high risk of cervical cancer or have mildly abnormal smears. It will have to be shown to be cost-effective to be used on a large scale.

Vaccine strategy for the future

The US Institute of Medicine's 1999 report *Vaccines for the 21st century: tools for decision making*, uses a cost-effectiveness model to develop a priority list of 26 vaccines for infections and chronic diseases in the USA. The model was based on vaccine impact on morbidity and mortality, the cost of health care for the illness, and the costs of the vaccine itself and its development.

The vaccines with the highest priority and feasibility were those for cytomegalovirus, influenza, group B streptococcus, and *S. pneumoniae*. Vaccines with a lower but still favourable rating were those for chlamydia, *Helicobacter pylori*, hepatitis C, herpes simplex virus, human papillomavirus, *Mycobacterium tuberculosis*, gonococcus, and respiratory syncytial virus (RSV).

In high income countries, new vaccine prospects are for rotavirus, conjugate pneumococcal vaccine, live attenuated influenza vaccines and vaccines for RSV and parainfluenza vaccines—all with potential impact on child health.

The reality in poorer countries, where 70% of childhood deaths are caused by infectious diseases, is that about half of these deaths could be prevented by better use of vaccines widely available in the developed world. For example, *Haemophilus influenzae* b and hepatitis B vaccines are not

available to most children in poor countries. Every child in the world, no matter where they live, should have access to vaccines that could immunize them against the major causes of death.

In arriving at a decision whether to immunize or not a public health organization measures the severity of the infection, the incidence of the disease, and the efficacy of the vaccine against the risk from the vaccine, and the price of the vaccine and the programme that will implement the vaccination campaign.

Non-parenteral routes and methods of vaccine administration

In most countries and most cultures, oral immunization is more readily accepted than vaccines that require injections. Moreover, the WHO Global Programme for Vaccines and Immunization has 'declared war' on unsafe injections with nonsterile needles and syringes, which in developing countries inadvertently transmit HIV, HBV and HCV from one infant to another. In fact the WHO estimates that worldwide more than one billion injections (not just vaccines) are given each year. Analysis at the WHO suggests that at least 50% of the injections given in some parts of the developing world are unsafe, and that more than 8 million HBV infections and almost 2 million HCV infections occur each year from unsafe injections.

Safer methods of vaccine administration have been developed. These include needleless devices that administer a liquid vaccine through the skin via a high-pressure air jet. A similar device uses high-pressure gas to deliver the vaccine in a powder form.

Another method of vaccine delivery under development involves the injection of a biosphere—a tiny starch ball, into the skin. It takes months to dissolve, thus releasing the vaccine steadily or in sudden bursts. The aim here is to avoid the need for booster injections.

Vaccines that preferably stimulate the mucosal immune response to provide an effective barrier against pathogens are highly desirable because mucosal surfaces are the most common site for pathogen entry, and because over 90% of all infections are acquired via mucosal routes. The mucosal immune system consists of molecules, cells and organized lymphoid structures intended to provide immunity to pathogens that impinge upon mucosal surfaces. Mucosal infection by intracellular pathogens results in the induction of cell-mediated immunity, as manifested by CD4-positive ($CD4^+$) T-helper type 1 cells, as well as $CD8^+$ cytotoxic T-lymphocytes. These responses are normally accompanied by the synthesis of secretory immunoglobulin A (S-IgA) antibodies, which provide an important first line of defence against invasion of deeper tissues by pathogens.

Recent advances in vaccinology have created new vaccines, antigen-delivery systems and adjuvants that can be administered via the mucosal surfaces by the rectal, vaginal, conjunctival, oral or nasal routes. The rectal route is highly efficient at eliciting immune responses but would be unpopular in several cultures, including Britain. The vaginal route excludes half the population. The conjunctival route leads on occasions to inflammation and purulent infection. Therefore, the oral and nasal immunizations are the most practical options. New generation, live, attenuated viral vaccines, such as the cold-adapted, recombinant nasal influenza and oral rotavirus vaccines have already been developed.

We already have three oral vaccines—polio, typhoid and cholera (the latter not yet available in the UK). Many other vaccines have been developed and are undergoing evaluation. A live attenuated influenza vaccine administered intranasally has been found to be safe, and effective when given to children in a USA study [Belshe R. *et al.* (1998) *N. Engl. J. Med.* 338, 1405–12].

The most exciting development in vaccine research has been the recruitment of plant science to the field. Two strategies have been used. One involves the integration into the host plant's chromosome of a microbial gene encoding an antigenic protein. A second approach exploits expression of a desired foreign gene that has been incorporated into the genome of a common plant virus. Once ingested, these bioencapsulated vaccines would release the antigen as food is degraded in the human gastrointestinal tract. Contact of the vaccine with the extensive gastrointestinal-associated lymphoid tissue could induce mucosal

immunity followed soon after by humoral mucosal immunity, secondary to the trafficking of lymphoid cells. Successful experiments have been carried out with potatoes and bananas.

Vaccination in utero may reduce vertical transmission of infectious diseases. Canadian scientists have introduced DNA herpes vaccine into the amniotic fluid of fetal lambs and elicited a powerful immune response to it. This approach may eventually reduce the need for Caesarian sections in women at high risk of passing on infections such as herpes and hepatitis to their offspring [*Nature Medicine* (2000) 6, 929–932].

Needle length

With the increased use of prefilled syringes with needles already welded to the syringe, there is a possibility of inappropriate placement of the vaccine, particularly in obese individuals. Already the UK Department of Health (DoH) recommends for deep subcutaneous and intramuscular immunizations the use of a 23G (blue) or 25G (orange) needle for infants, and 23G (blue) for adults.

The US Advisory Committee on Immunization Practices (ACIP) recommends that 'the needle should be long enough to reach the muscle mass and prevent the vaccine from seeping into the subcutaneous tissue' [the ACIP for the Centers for Disease Control and Prevention (USA) (CDC)] publishes statements for each recommended childhood vaccine: http://www.cdc.gov/nip/publications/aciplist.htm). Furthermore, it recommends that 'an individual decision on needle size should be made for each person based on age, volume of drug, size of the muscle and the depth below the muscle surface into which the material is to be injected'. The Australian advisory body recommends the longer needle for all but very small infants so that the vaccine can reach the substance of the muscle.

If the needle is too fine, the vaccine may not dissipate over a wide enough area. If the needle is too short, it may not enter the muscle and especially the bulk of the muscle. Such poor technique or inappropriate needle size may result in sometimes severe local reactions and/or the vaccine may not take. Aluminium-adsorbed vaccines should be given by the intramuscular route because subcutaneous or superficial administration leads to an increased incidence of local reactions.

In a paper published in 1997 [Gregory A. *et al.* (1997) *J. Am. Med. Assoc.* 277, 1709–11] researches surveyed the deltoid fat pad thickness. Using ultrasound measure-ments of the skin and fat thickness overlying the deltoid, the research team confirmed that deltoid penetration to a depth of 5 mm was only possible using:

- 1 inch (25 mm—23G blue) needle in men between 59 and 118 kg;
- 5/8 inch (16 mm—25G orange) needle in women less than 60 kg;
- 1 inch (25 mm—23G blue) needle in women between 60 and 90 kg;
- 1.5 inch (37.5 mm—21G green is 40 mm) needle for women over 90 kg.

By implication, according to data presented in that paper, for children we need to use the 5/8 (16 mm—25G orange) needle length.

Researchers from the Oxford Vaccine Group at the University Department of Paediatrics, John Radcliffe Hospital, studied redness, swelling and tenderness at the injection sites of 119 healthy infants, following their routine 16-week (third) DTP and Hib immunizations. The study was conducted in eight general practices in Buckinghamshire. 61 infants were vaccinated with the shorter, 25G orange hub needles, and 58 with the longer 23G blue hub needles. After six hours, the longer (blue) needle group suffered only two-thirds the rate of redness, and one-third the risk of swelling of those injected with the shorter (orange) needles. Three days later, the rate of redness with the blue needles was only one-seventh of the orange needle group, with the rate of swelling still one third. Rates of tenderness were also lower with the longer needle throughout follow up, but the difference was not statistically significant.

The researchers concluded that the use of the 25G blue needle significantly reduced rates of local reaction to routine infant immunization. On average, for every five infants vaccinated, use of the longer needle instead of the shorter needle would prevent one infant from experiencing any local reaction [Diggle L., Deeks, J. (2000) Effect of needle length on incidence of local reactions to

routine immunisation in infants aged 4 months: randomised controlled trial. *BMJ* 321, 931–933].

When a vaccine with a needle welded to the syringe is licensed, it has to demonstrate that the vaccine given with that needle, at the recommended site, is immunogenic. The doctor or nurse should ensure that the vaccine is given to the licensed site (e.g. deltoid or anterolateral thigh). In this case, there are no fears that the vaccine will not 'take', provided that the operator is skilled. If no needle is supplied with the vaccine, a (25 mm) 23G blue needle should be used, but consider a (37.5 mm) 21G green needle for all those over 90 kg. Practically, this means that children and a large number of adults will receive their immunizations using a blue needle. For very small infants a (16 mm) 25G orange needle may be used.

The WHO recommends the 23G blue needle be used for all infant vaccinations. It also recommends the following injection technique in order to ensure the vaccine is delivered to the muscle.

1 The thumb and forefinger should be placed on the anterolateral thigh.
2 The skin should be stretched flat between finger and thumb.
3 The 23G blue needle should be pushed quickly straight down through the skin between the finger and thumb, deep into the muscle.

Topical anaesthesia before injection

The eutectic mixture of local anaesthetic (EMLA) cream, which is applied topically under an occlusive dressing, has been evaluated in multiple placebo-controlled, randomized trials and has been demonstrated to provide pain relief during injection. It required one hour to work adequately but, in my practice, a few minutes will suffice.

Site of vaccine administration—multiple injections

Apart from BCG, all parenteral vaccines are given by intramuscular or deep subcutaneous injection. The preferred site is the anterolateral thigh (high up) in infants. Beyond this age (see below), the deltoid muscle is the preferred site for injections.

The gluteal muscle (buttock) should not be used for the administration of vaccines. There is past evidence of sciatic nerve damage from immunizations given into the buttock. Furthermore, the plentiful adipose tissue at that site (especially in infants that have not as yet walked to develop their gluteal muscle) can reduce the absorption and efficacy of administered vaccines. This is particularly true for rabies, hepatitis A and hepatitis B vaccines. The buttock can be a dirty area with a risk of infection and formation of subcutaneous fibrous nodule. The British Paediatric Association recommends either the anterolateral thigh or deltoid.

When more than one vaccine needs to be injected at the same time, they should be given on contralateral thighs or deltoids—depending on age. Live-virus vaccines must be given simultaneously and on different sites. This way antibody response is not impaired and the rate of adverse events is not increased. Otherwise, they should be separated by a time period of 3 weeks.

Inactivated vaccines can be given either simultaneously or at any time before or after another inactivated or a live-virus vaccine. Ideally, each recommended site should receive one injection. In the event where you have more than two injections to give on one site, the live-virus vaccines should be given on contralateral sites and the inactivated vaccines should be either postponed for later or given about 1 cm away from another vaccine.

With regard to children and intramuscular vaccinations, the following 'rule of thumb' may be applied:

- under 1 year of age the anterolateral thigh is the preferred site;
- between 1 and 6 years of age the anterolateral thigh or the deltoid are suitable;
- over 6 years of age the deltoid is the preferred site.

Interchangeability of vaccines

Similar vaccines made by different manufacturers are considered interchangeable when administered according to their licensed indications. Whenever possible a primary immunization course or booster

should be completed with the same vaccine used initially. There may be situations when:

- the brand name of the vaccine used previously is not known;
- the vaccine is not currently available in the Travel Clinic;
- the vaccine is not available due to manufacturing delays or production problems; or
- the vaccine has been withdrawn from the market.

In such cases, it is acceptable to use another manufacturer's similar schedule vaccine, in order to complete the primary course or for a booster dose.

Revaccination after adverse reaction

In an Australian study [Gold M. *et al.* (2000) Re-vaccination of 421 children with a past history of an adverse vaccine reaction in a special immunization service. *Archives of Disease in Childhood* 83, 128–31) 469 children had an adverse event: 63% had a local reaction, fever or irritability, while 37% had a hypotonic hyporesponsive episode, convulsions, rash or anaphylaxis. In 90% the reaction was associated with DTP vaccine, and 10% with acellular pertussis, MMR, Hib, OPV, hepatitis B, combined diphtheria and tetanus.

After review, 90% were re-vaccinated. Acellular pertussis was given if the reaction involved the whole-cell vaccine. Of all the re-vaccinated children, 83% had no adverse reaction, 17% had fever and/or a local reaction, and only one had a significant episode, but made a full recovery.

Chapter 4

The cold chain and vaccine storage

'Cold chain' is the maintenance of vaccine and immunoglobulin potency by maintaining the manufacturer's recommended temperature (+2–+8 °C) during storage and distribution from the manufacturer to the user. The previous Medeva oral poliomyelitis vaccine (Evans OPV), which required temperatures of 0 to 4 °C, is not available in the UK. All immunoglobulins require temperatures of 2 to 8 °C. Temperatures above or below the above will cause deterioration of the vaccine or even breakage of the glass vials or syringes if they should freeze.

One person (with a deputy) in the practice/clinic should be designated to have overall responsibility for the care of the vaccines.

- Sufficient supplies of vaccines should be ordered, taking care to avoid stockpiling. Expiry dates on existing vaccine stocks should be checked and brought forward to be used first. Date-expired vaccines should be removed.
- On receipt of vaccines, they should be checked, recorded and refrigerated immediately.

The vaccines refrigerator should not be a domestic one but a special pharmacy refrigerator, which is of a higher specification and may incorporate an internal fan, an external thermometer and should have an external lock. Larger practices should consider a large pharmacy refrigerator for vaccine stocks and a small one in the treatment room for everyday vaccinations. Nothing other than vaccines should be stored in the practice pharmacy refrigerator, and in particular no food.

- The vaccines refrigerator should be supplied from a switchless electrical socket. If this is not available, protect the socket with tape or something similar to avoid accidental switching off, and label it clearly.
- Avoid opening the refrigerator door unnecessarily and, once opened, close the door as soon as possible. Consider locking the refrigerator when it is not in use.
- Defrost the refrigerator regularly if it has no automatic defrost. Keep vaccines in another refrigerator or cool box while doing this.
- Consider an internal maximum/minimum thermostat, even if there is an external thermometer fitted to the refrigerator. Some are able to record the maximum and minimum temperatures achieved.
- Keep a notebook close to the refrigerator and record the daily temperatures as well as the maximum and minimum temperatures reached, if possible. In case of refrigerator failure or electricity interruption, seek advice from the local community services pharmacist or the Drug Information Centre. Failing this, consider contacting the vaccine manufacterer/s.
- Inside the refrigerator, the vaccines should not be stored too tightly. Air should be allowed to circulate around the packages. No vaccines should be stored in such a way that they could come into contact with ice. Avoid shelves or storage compartments on the refrigerator door—this is especially important if, against good clinical practice, a domestic refrigerator is used.
- Reconstituted vaccines must be used within the manufacturer's recommended period—usually 1h but some are viable up to 4h. Unused vaccines and opened multidose vials should be discarded, although the oral polio multidose vaccine may be re-refrigerated and re-used for a short time, usually the same morning or afternoon (manufacturers advice). The DoH advises up to 4 weeks when the OPV is stored at appropriate cold chain conditions and is in date. Unused whole vials that have been left out of the refrigerator for any appreciable length of time, are out of date or frozen, should also be discarded.
- Remove vaccines from the refrigerator just before the beginning of a vaccination session and

return them to the refrigerator as soon as possible, and not later than 3 hours, after. Remove only the required number of vaccines. Unused vaccine that is put back in the refrigerator should be used first at the next immunization session as repeated warming and cooling of vaccines shortens their shelf life.

- Some vaccines need to be protected from light, e.g. OPV, BCG, reconstituted MMR.
- Vaccine in an already opened ampoule can be destroyed by soaking it in hypochlorite solution for 20 min (e.g. Milton). Such treated ampoules can then be discarded into the Sharps bins.
- Partly used vials should be stored in a marked container and returned via the Pharmacy Collection Service for unused medicines.
- Empty vials should be discarded into a Sharps bin.

The supply of vaccines is through an appointed distribution service (e.g. Farillon Ltd), the local pharmacy, a courier service, or by post from the manufacturer. If vaccines are sent by post, check the dispatch date and time. They should not be accepted if posted more than 48 h prior to receipt. If in doubt, do not accept. Where coolboxes or insulated containers are used, the vaccines should not come into contact with frozen ice packs.

In case of disruption of the cold chain (electricity supply interruption, accidental switching off of the refrigerator etc.), and before seeking advice from the local community services pharmacist, the local Drug Information Service or the manufacturer, be prepared to answer questions including:

- How long has the refrigerator been off?
- What are the last minimum/maximum recorded temperatures?
- What is the temperature around the outside of the refrigerator?
- What vaccines are in the refrigerator, including their manufacturers?
- When will the clinic need and which vaccines?

Do not discard any vaccines until expert advice is taken. The thermostability of the vaccines varies. For example, at room temperature (21°C) the potency of the Fluarix (SKB) vaccine is not affected for one week, while that of polio (SKB) vaccine is 2 days.

For advice on supplies of *refrigeration equipment and accessories* telephone the Communicable Disease Branch at the DoH on 020 7972 1430.

Insulated containers for vaccine transport are available from Thermos Ltd (Tel.: 01277 213 404) and Mailbox International Ltd (Tel.: 0161 330 5577).

For active *temperature management system combined with continuous monitoring containers* contact ISOsafe Ltd, Woodlands Business Village, Basingstoke, Hants, RG21 4JX (Tel.: 01256 362 700. Fax: 01256 869 911).

Chapter 5

Transmission of infection

Infection can be transmitted from patients suffering active infection as well as from carriers. Diseases that spread to humans from animals are called zoonoses.

Horizontal spread occurs between people in the same population, and person-to-person is the most common method.

Vertical spread is where infection is passed on from mother to fetus (congenital rubella, hepatitis B).

Infection spreads by one of the methods detailed below.

Inhalation

Infected droplets from the respiratory tract, mouth, throat and nose are expelled during coughing, sneezing and speaking, and these are then inhaled by the new host. Diseases that may spread this way are whooping cough, influenza, pulmonary tuberculosis, diphtheria, mumps, measles, rubella, chickenpox and scarlet fever.

Ingestion

The pathogens present in the faeces, vomit, urine or respiratory secretions contaminate hands, fingers, cooking and eating utensils, clothing, toilets, etc. Diseases that spread this way are typhoid, cholera, hepatitis A and E, salmonellosis, dysentery and poliomyelitis. A common form of transmission is direct contact between faecally contaminated hands and oral mucosa (faecal–oral transmission). Another way is by ingestion of contaminated food, e.g. brucellosis, *Campylobacter* enteritis and salmonellosis. Food-borne transmission is most likely to occur if contaminated food is eaten raw or undercooked. It is important that milk is pasteurized, water is supplied by reputable organizations and a very good sewage system is in place.

Inoculation/direct contact/bites

Pathogens can be inoculated directly into the body through a defect in the skin, can penetrate the mucosal surfaces or are introduced via a bite. Examples are hepatitis B virus (HBV), human immunodeficiency virus (HIV), malaria, anthrax, tetanus, rabies, leptospirosis (if the urine of infected animals contaminates fresh water or swimming facilities).

Venereal route

The pathogen is transmitted by sexual contact, e.g. HBV, HIV, herpes genitalis, syphilis, gonorrhoea, lymphogranuloma venereum.

Iatrogenic

Infection can be transmitted from contaminated gloves, instruments, transfusions, blood, blood products, nonsterile needles or syringes, e.g. HBV, HCV, HIV, malaria. Iatrogenic is from *iatros*, Greek for doctor.

Vectors

Some living creatures are able to transmit infection from one host to another, and they are called vectors. Important vectors in humans are:

- mosquito—malaria, yellow fever, Japanese B encephalitis, dengue fever, filariasis;
- tick—relapsing fever, encephalitis, typhus, Lyme disease;
- flea—plague, rickettsial infection;
- louse—typhus, relapsing fever;
- sandfly—sandfly fever, leishmaniasis;
- fly—trypanosomiasis, onchocerciasis;
- mite—typhus, scabies;
- cone-nosed bug—Chagas' disease.

Fomites

Objects on which pathogens are transported from source to host, i.e. bedding, towels.

Chapter 6

Infectivity and exclusion period of infections

Infection	Infectious	Exclusion
Chickenpox and herpes zoster	2 days before to 6 days after spots develop	Until all spots have crusted
Hepatitis A	Several days while asymptomatic until 7 days after onset of jaundice	Until 7 days after onset of jaundice and the patient feels well
Hepatitis B	Not infectious under normal work/ school conditions	Until patient is well
Impetigo	While spots discharging pus	Until spots have healed
Measles	A day before onset of symptoms and until 5 days after rash appears	Until the child feels well—minimum 4 days from onset of rash
Mumps	7 days before and until 9 days after the swelling appears	Until child feels well—minimum 9 days from onset of swelling
Pertussis	4 days before and until 21 days after the start of cough or until 6 days after antibiotic therapy started	5 days from starting antibiotic therapy
Rubella	1 week before and until 1 week after onset of rash	Until 7 days after rash appears
Scarlet fever	As sore throat starts, until the second day after antibiotic therapy started	Until the second day after antibiotic therapy started
Tuberculosis	When sputum cultures are positive. After 2 weeks of antibiotic therapy	After 2 weeks of antibiotic therapy

As a general rule, food handlers presenting in general practice with diarrhoea should be excluded from work until they are symptom-free and for 48 h afterwards.

Chapter 7

Immunization in practice

Immunization coverage

The immunization coverage represents the proportion of people that have been vaccinated. The WHO target for immunization coverage of children at 2 years of age is 95%.

The fifth objective of the Health for All in the Year 2000 programme of WHO-Europe states: 'By the year 2000, there should be no indigenous cases of poliomyelitis, diphtheria, neonatal tetanus, measles, mumps and congenital rubella in the region, and there should be a sustained and continuing reduction in the incidence and adverse consequences of other communicable diseases, notably HIV infection.' This objective has not been met. All 15 countries of the European Union have ratified this objective. Figure 7.1 shows the reported immunization coverage in Western European countries. This figure was prepared with kind assistance from Aventis Pasteur MSD and the source is the vaccine-preventable disease monitoring system of the WHO.

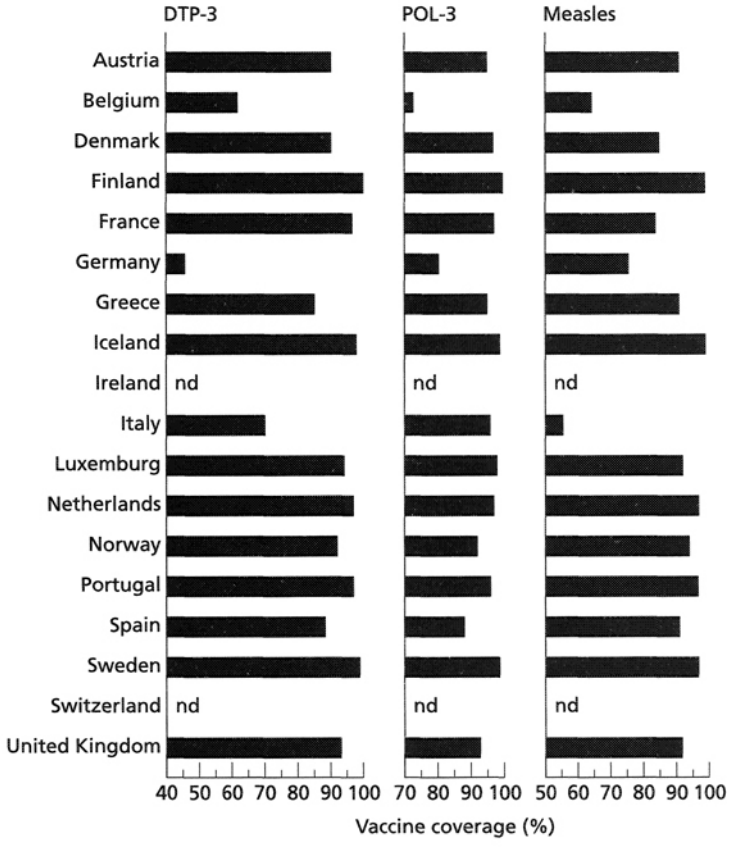

Fig. 7.1 Immunization coverage (percentage) of children aged less than 2 years in Western European countries. DTP (diphtheria/tetanus/whole-cell pertussis combined vaccine), POL, (poliomyelitis), both 3 doses and one dose of measles vaccine, 1996–1998.

As yet, there is no standardization of measuring techniques in practice in all the countries of the European Union. This is particularly a problem in countries where vaccination is also carried out by the private sector.

Uptake of childhood immunization

Uptake of childhood immunization reached its highest level ever in England in 1996/97. Uptake of three doses of DTwas 97%, three doses of pertussis 94%, *Haemophilus influenzae* b 94% and MMR 92%. The 'MMR scare' (see Chapter 22) has had a negative effect on the uptake of childhood immunizations in the UK with an overall drop. In the year 1997/98 the uptake among those reaching their second year of life was 96% for DT and polio, 95% for Hib, 94% for pertussis and 91% for MMR. The uptake for MMR in England continued to fall and was at its lowest level (87.6%) in the first quarter of 1999. It then rose for the first time in 2 years to 88% in the second quarter of 1999, still well away from the necessary 95%.

The achievement of high standards of immunization coverage depends on many factors, as shown in Fig. 7.2.

The aim of the Primary Healthcare Team

The aim through immunization is to protect the community as well as the person vaccinated from infectious diseases. This we try to achieve as early as possible, hence the DTP–OPV–Hib-MenC course is started in the UK at the age of 2 months old.

Sometimes the benefit of immunization is only to the vaccine recipient as in the case of tetanus. Most of the time immunization of individuals aims to achieve sufficiently higher coverage (*herd immunity*) to interrupt transmission into the community. This way both immunized and non-immunized individuals benefit.

Herd immunity is the basis on which all national immunization programmes are designed. The concept here is that not everyone in a population needs to be immunized in order to protect that population. As long as sufficient numbers of children are immunized against a specific disease the protection can extend to everyone. What is important is to find the percentage of the population that must be immunized for herd immunity to be created. This depends on:

- the infectivity of the disease (protection against the highly infectious measles will require a higher percentage of children to be immunized than for the less infectious mumps);
- the susceptibility of the population (has the infectious disease been circulating in the community and for how long?);
- vulnerability of the population (overcrowded inner city against a sparsely populated rural area);
- environmental factors (the disease may be more prevalent during one season of the year than

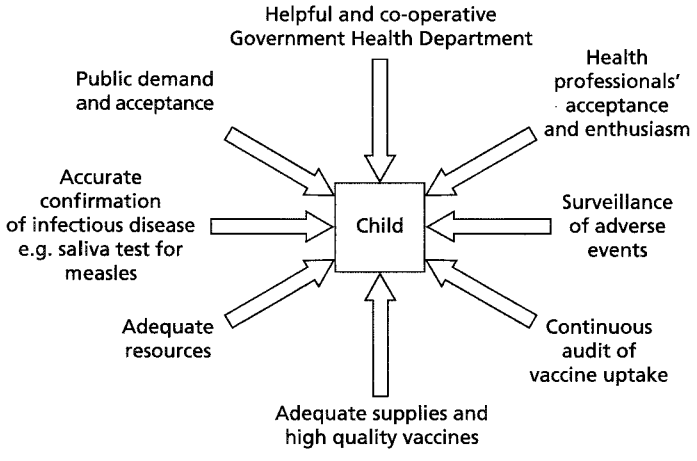

Fig. 7.2 Factors influencing the achievement of high immunization coverage.