The basics of viral vaccines

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Abstract

The family practitioner plays an important role in preventing disease. An estimated two million people die globally from vaccine-preventable diseases each year. Immunisation of children does not only benefit the immunised children, but also their contacts and the community at large. Selective vaccination of adults should be a speciality of every family practitioner. This article discusses the principles of immunisation against hepatitis, mumps, measles, rubella, chickenpox, poliomyelitis, yellow fever and influenza.

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Introduction

Viral vaccines are one of the success stories of medicine. The impact of vaccines on disease prevalence and prevention cannot be matched by any other healthcare-related intervention. The most dramatic of these was the eradication of smallpox in 1979.[1] Poliomyelitis was the second disease earmarked by the WHO for eradication by 2005. This target was not reached, however, since nearly 2 000 cases have been reported worldwide over the past year.[2] Measles is the third disease that is targeted for eradication.[3]

With an estimated two million people dying from vaccine-preventable diseases each year, it is fitting that the Bill Gates Foundation has given a total of $1,5 billion for the development and distribution of these life-saving vaccines. Immunisation of children does not only benefit the immunised children, but also their contacts and the community at large through the establishment of herd immunity, which limits the circulation of wild viruses. The general terms and definitions used in this article are listed in Table I.

Vaccine constituents

Suspending fluid is needed in addition to the immunogenic virus or viral antigen. This may be simple saline, but it may also contain proteins derived from the medium in which the vaccine was produced, e.g. eggs or

Table I: Definitions

Immunisation: The induction or provision of immunity against an infection or disease. This induced immunity may prevent or suppress infection.
Active immunisation: The host's immune response is induced through the administration of a live attenuated or inactivated virus or part of a virus. This implies the formation of memory cells and the potential for lifelong protection, which may take days to weeks to be established.
Passive immunisation: Preformed antibodies are administered and no immune response is raised. Immunoglobulins provide immediate protection for a maximum of three to four months.
Active-passive immunisation: When both active and passive immunisation are administered together. This is only done in a few situations, e.g. post-exposure for hepatitis B in a non-immune individual and after possible exposure to rabies.
Therapeutic vaccination: Immunisation, which leads to suppression of infection and thus retardation of disease. Strategies against HIV, hepatitis B, hepatitis C, human papillomavirus and herpes simplex virus are currently under investigation.
Herd immunity: An additional form of protection achieved through active vaccination of a significant proportion of the at-risk population. By increasing the number of individuals who cannot contract and consequently cannot transmit a disease, a measure of protection is achieved for non-immunised persons by default.

Table II: Immunoglobulins available in South Africa

Normal human immunoglobulins
- Prophylaxis for measles and hepatitis A (IM) - Intragam®, Beriglobin®
- HIV-positive children with repeated infections (IV) - Polygam®

Specific hyperimmune globulins
- Hepatitis B immunoglobulin - Hebagam®
- Rabies immunoglobulin - Rabigam®
- Varicella-zoster immunoglobulin - Vazigam®

Monoclonal antibodies
- Respiratory syncytial virus (Palivizumab) - Synagis®

IM = intramuscular, IV = intravenous

cell culture. Preservatives or stabilisers are added, e.g. thimerosal or gelatine, as well as antibiotics like neomycin. Adjuvants are substances that are added to vaccines to enhance their immunogenicity. Hypersensitivity reactions to any of these components can occur.

Passive immunisation

Normal human immunoglobulins are general antibodies obtained from the adult blood donor population. The locally manufactured Intragam® and Polygam® are believed to have protective levels of antibodies against hepatitis A and measles due to the high prevalence of these infections in South Africa. Formulations such as Beriglobin®, which are manufactured in Germany, have much lower concentrations of these antibodies than the local products. Normal immunoglobulins are used for immediate post-exposure protection against measles and hepatitis A. They can also be used for pre-exposure prophylaxis for hepatitis A in travellers. Specific immune globulins are obtained from donors recently immunised or in the convalescent phase after natural infection (see Table II). For the best protection, immunoglobulins must be given as soon as possible after exposure. After 48 to 72 hours, the protective effect decreases dramatically. Immunoglobulins may impair the efficacy of live attenuated virus vaccines, therefore they should not be administered 14 days before or three months after immunoglobulin administration.

Palivizumab is a humanised monoclonal antibody recommended for prophylaxis in premature babies or those with chronic lung disease to reduce the severity of RSV infection.[4] Monthly intramuscular injections are given during the RSV season (March to July), but are extremely expensive (R5 000 or more per dose).

Active immunisation (see Table III)

Live attenuated vaccines

As a general rule, these vaccines induce humoral and cellular immunity with durable protection, similar to protection after primary natural infection. The transport, storage and delivery of these vaccines are critical. Their temperature should be maintained between 2 and 8 °C and they must never be frozen.

Table III: Viral vaccines available in South Africa

Live attenuated vaccines
- Measles - Diplovac®, Rouvax®
- Rubella - Rudivax®
- Mumps, measles, rubella (MMR) - Morupar®, Priorix®, Trimovax®
- Chickenpox - Varilix®
- Poliomyelitis (oral polio vaccine) - OPV-Merieux®, Polioral®, Polio Sabin®
- Yellow fever - Stamaril®

Inactivated vaccines
- Hepatitis A - Havrix 1440®, Havrix Junior®, Avaxim®
- Hepatitis B - Engerix-B®, H-B-Vax II®, Heberbiovac HB®
- Hepatitis A and B - Twinrix®
- Influenza - Agrippal®, Influvac subunit®, Mutagrip®, Vaxigrip®
- Rabies - Rabipor®, Verorab®
- Poliomyelitis (IPV) - Constituent of TdPolio®

Inadvertent repeat immunisation with these vaccines merely boosts the active immunity and is not associated with deleterious side effects.

No live vaccine should be administered to pregnant women because of the theoretical risk of possible harm to the foetus. The current recommendation is to administer live attenuated vaccines to all asymptomatic HIV-positive children[5] and HIV-positive adults[6] with CD4+ T lymphocyte cell counts >200/ml.[3] The potential benefit must be weighed against the potential theoretical increased risk

Specific viral vaccines and immunoglobulins (see Tables IV and V)

Table IV: Current recommended immunisation schedule for infants and children in South Africa[7]

Age	BCG	OPV	DTP	Hep B	Hib	Measles	DT
Birth	BCG	OPV					
6 weeks		OPV	DTP	Hepatitis B	Hib		
10 weeks		OPV	DTP	Hepatitis B	Hib		
14 weeks		OPV	DTP	Hepatitis B	Hib		
9 months						Measles	
18 months		OPV	DTP			Measles	
5 years		OPV					DT

BCG = Bacille Calmette-Geurin against tuberculosis, OPV = oral polio vaccine, DTP = diphtheria, tetanus and pertussis, Hib = Haemophilus influenzae type b, DT = diphtheria and tetanus

Table V: Additional viral vaccines available in the private sector for infants and children

Age	Vaccine			
1 year plus	VZV			
15 months		MMR*		
12 months			Hepatitis A	
12½ months			Hepatitis A	
4-6 years	VZV	MMR		
Yearly				Influenza

* This MMR dose will replace the measles dose at 18 months (see text)
VZV = Varicella zoster virus, MMR = mumps, measles and rubella

in each individual patient. Children on cytotoxic therapy or long-term cortisone therapy should not receive live vaccines. Where possible, the child should be immunised prior to the initiation of immunosuppressive therapy.[6] The immune response to a live vaccine may be impaired if administered within 30 days of another live vaccine. For optimal response, live vaccines must either be given at the same time or 30 days apart.[6]

Inactivated vaccines

Killed virus vaccines may be whole viruses, split particles of a virus or specific fragments (subunits) of a virus. These vaccines are not as immunogenic and generally require a primary series of two to three injections at spaced intervals and boosters every one to five years to maintain protective antibodies. Inactivated vaccines do not interfere with other inactivated or live vaccines and can be administered simultaneously.[6]

Hepatitis B

Immunisation against hepatitis B has been part of the routine immunisation schedule in South Africa since 1995. Adult vaccination is recommended for at-risk persons, e.g. healthcare workers, hospital support staff at risk of exposure, haemodialysis and haemophiliac patients, sexual partners of chronic carriers and those with high risk sexual practices, and IV drug users. The course consists of three doses at monthly intervals or at nought, one and six months. Five to ten per cent of patients may fail to develop serologically detectable antibodies if tested one to three months after the primary series of injections.[8] These "non-responders" should receive an additional vaccination dose or, if they still do not respond, an additional vaccination course. Those with risk factors for non-response (older than 30 years, obesity or immunodeficiency) should receive a double vaccine dose (40 µg). There currently is controversy regarding the need for five yearly boosters. It is believed that the protection is nearly 100% in persons with antibody levels above 10 mIU and boosters therefore are indicated only in individuals with undetectable antibodies.[8]

Hepatitis B hyperimmune globulin is indicated for post-exposure prophylaxis after a needle-stick injury in a non-immune individual, in a sexual partner of an active case of hepatitis B or in neonates born to HBsAg-positive mothers. In these cases, the course of active vaccination must be administered at the same time.[8]

Table VI: Indications for influenza vaccine use in South Africa

- Persons who are at high risk for influenza and its complications because of underlying medical conditions and who are receiving regular medical care for conditions such as
  - Chronic pulmonary disease
  - Chronic cardiac disease
  - Chronic renal disease
  - Diabetes mellitus and similar metabolic disorders
  - Immunosuppressed individuals (including HIV-infected persons with CD4+ counts above 200 cells/ml)
- Residents of old age homes, chronic care and rehabilitation institutions
- Children on long-term aspirin therapy
- HIV positive children
- Medical and nursing staff responsible for the care of high-risk cases
- All persons over the age of 65 years
- Women who would be in the second or third trimester of pregnancy during the influenza season
- Any person wishing to protect themselves against the risk of contracting influenza, especially in industrial settings

Hepatitis A

Vaccination for hepatitis A is recommended for susceptible persons travelling to endemic areas where food or water may be contaminated with faecal material. Other at-risk individuals include sewage workers, healthcare workers, people working with young children and children at twelve months of age.[9] A booster dose must be given six months after the primary dose. For post-exposure prophylaxis, immediate active immunisation seems to be better than passive immunisation.[10]

Influenza

Since the antigenicity of influenza viruses is constantly changing (antigenic drift), vaccines are annually reformulated to represent the current circulating strains of influenza A and B. Vaccines contain two influenza A strains and one influenza B strain and are manufactured specifically for the Southern or Northern hemisphere flu seasons. The following strains have been recommended by the World Health Organization (WHO) for South Africa in 2006: A/New Caledonia/20/99(H1N1)-like virus, A/Califoria/7/2004(H3N2)-like virus and B/Malaysia/2506/2004-like virus. The vaccine should be administered annually from March to April (see Table VI). Children aged six months to three years should receive half of the standard dose, while children younger than nine years who have never been vaccinated before should receive a second dose after four to six weeks.[11] Influenza vaccine is also recommended for HIV positive children.

Measles

Vaccination against measles is recommended for all children at nine and eighteen months of age. The mumps, measles and rubella (MMR)

vaccine can be given at 15 months instead of the measles vaccine at 18 months. Vaccination at six months is only recommended for HIV-positive babies[5] or if there is an outbreak in the community.[12] Hypersensitivity to egg protein is not a contraindication to vaccination. A measles-like rash about one week after vaccination is occasionally seen (not common). It is a benign side effect and not contagious. Neurological complications due to the vaccine occur in less than one per million doses administered. This must be compared to the high fatality rate of measles in developing countries, where an estimated more than one million children died of the disease each year prior to increased vaccination attempts launched by the WHO in 1998.[13] Due to increased measles immunisation in the developed world, the mortality came down by 60% by the end of 2004.[14]

There were reports of an increased rate of autism linked specifically to MMR immunisations in the late 1990s. Subsequent investigations did not show any evidence to support these claims.[15]

Rubella

Vaccination against rubella is advised at 15 months (mostly as part of the MMR vaccine). Non-immune girls aged 10-12 years or woman of childbearing age must also be vaccinated to prevent congenital malformations associated with rubella infection during pregnancy. Vaccination is contraindicated during pregnancy and pregnancy must be avoided in the three months following vaccine administration. Analysis of data from several countries did not show an increased risk for foetal malformations when rubella vaccine was inadvertently administered during pregnancy and therefore accidental administration is no longer regarded as a reason for termination of pregnancy.[16] Athralgia occurs in 3% of vaccinated children and 12 to 20% of adult women.

Varicella-zoster (chickenpox)

Vaccination against chickenpox is indicated in children from one year of age and to susceptible high-risk patients and their healthy contacts.[13] Patients older than 13 years must get two doses six months apart. Breakthrough varicella after vaccination has been described, but is much less severe than chickenpox. It occurs most commonly if the vaccine was administered before one year of age or in individuals vaccinated more than five years previously.[17] Universal vaccination of children in the USA was associated with a sharp decline in the death rate due to the disease.[18] Vaccination can also be attempted in elderly patients with recurrent shingles to boost the natural immune response.[19]

Varicella-zoster immunoglobulin is indicated to provide protection against varicella in high-risk exposed immunocompromised patients and neonates. It is not indicated for the treatment of chickenpox or zoster.

Poliomyelitis

Reversal to the virulent type of the oral live attenuated polio vaccine (OPV) strain causes vaccine-associated paralytic poliomyelitis (VAPP) in one per 2.4 million vaccinated people. This occurs more frequently in adults, immunodeficient persons and those receiving their first dose of OPV.[20] Due to its reduced cost and ease of administration, OPV is used in the developing world for childhood immunisation. OPV contains the live attenuated strains of all three poliovirus serotypes. Since faecal shedding occurs in vaccinated people, unvaccinated contacts could also be vaccinated, especially in areas with poor hygienic conditions.[21] This also implies that viral shedding of the mutated virus may (very rarely!) lead to VAPP in unvaccinated contacts, particularly the immunosuppressed.[13] It therefore is prudent that all unimmunised parents whose babies are given OPV be immunised with IPV. There is, however, not a policy in South Africa of giving IPV to unimmunised adults whose babies are given OPV. The inactivated poliovirus vaccine (IPV) is currently used for routine childhood administration in the USA, Australia and other European countries,[22] and is indicated in non-immune adults travelling to endemic areas.

Rabies

Routine immunisation against rabies is only given to people at risk, e.g. veterinarians and abattoir workers. A series of three doses is administered on days 0, 7 and 28, with boosters recommended every three to five years. The management of possible exposure to rabies encompasses proper wound cleaning, passive immunisation with human antirabies immunoglobulin (RIG) on the day of exposure (day 0), and the initiation of a five-dose series of active immunisation on days 0, 3, 7, 14 and 30. All bite wounds should be flushed with water or an antiseptic (if available) for five to ten minutes. Bleeding should be encouraged and wound suturing should be avoided or delayed. An iodine-based disinfectant or 70% alcohol must be applied to the wound after cleaning. The complete dose of human RIG preferably should be infiltrated into the wound or surrounding tissue. Where this is not possible, the remaining RIG may be injected in the nearest deltoid muscle. With multiple wounds, the dose may be diluted up to 50% in saline to allow infiltration of all the wounds. The vaccine must be administered in the deltoid and not in the gluteal area.[23]

Yellow fever

The yellow fever vaccine was approved by the FDA in 1953. Adverse effects among the elderly may be much higher and the risk must be weighed against the benefit for these travellers.[24] This vaccine may only be administered by doctors or travel clinics with special certificates obtained from the HPCSA. People travelling to or from endemic areas (West and Central Africa and South America) should be vaccinated. Although immunity is thought to be life long, international health regulations required that a booster dose is administered every 10 years for travel to and from endemic countries.[25] Vaccination is contraindicated in children younger than nine months, during pregnancy and lactation, in the severely im-

munocompromised, i.e. HIV-positive patients with CD4+ T lymphocyte cell counts <200/ml, and in people with egg hypersensitivity. An exemption certificate can be obtained for these groups of people if travel to an endemic region is necessary.[26]

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Ⓟ This article has been peer reviewed

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