VACCINATION AGAINST VIRAL DISEASES

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World Health Organization

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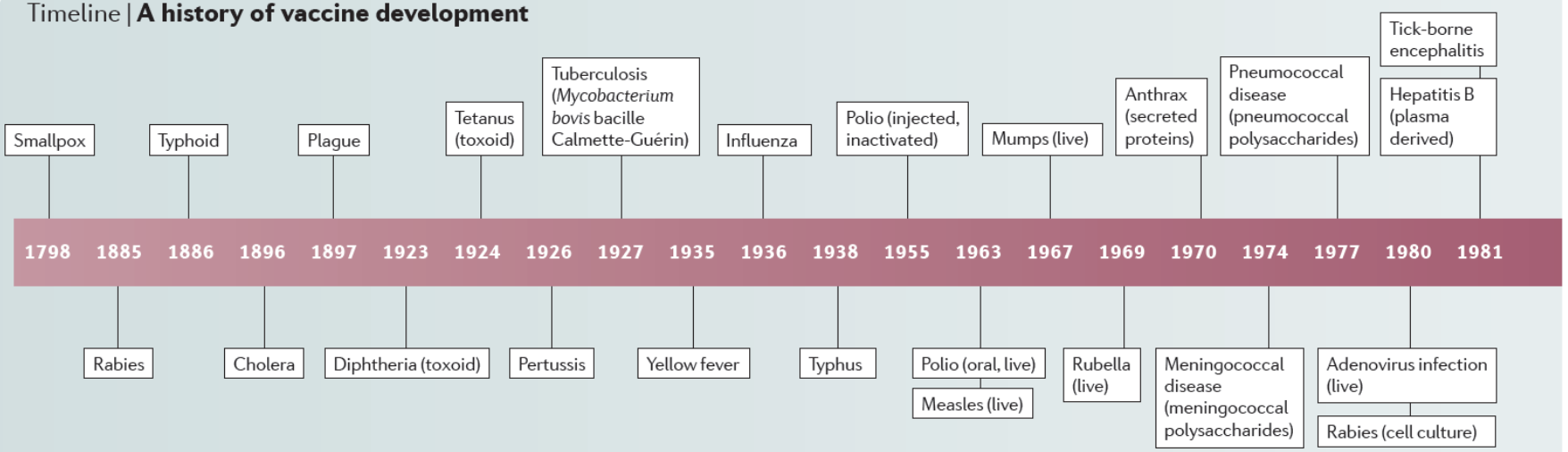
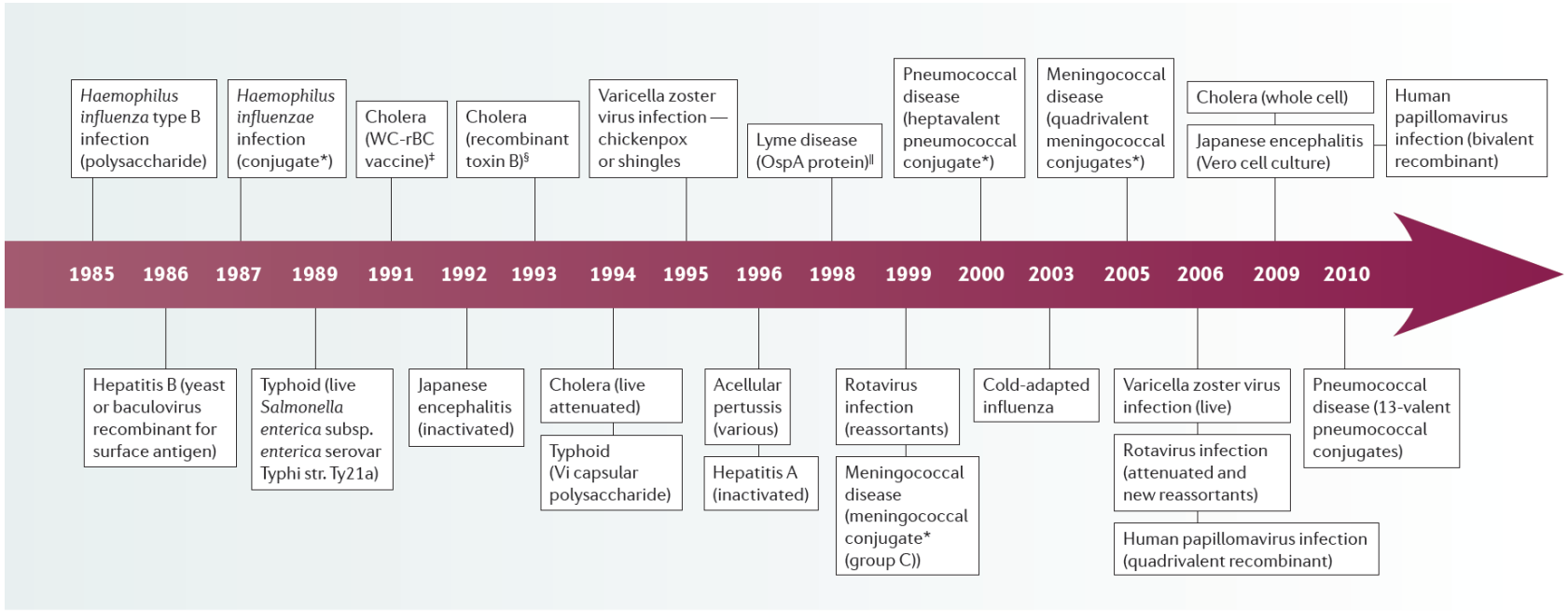
Vaccines have proved to be one of the most powerful and effective ways of reducing disease and vaccination is considered the most cost-effective medical intervention ever introduced

Timeline | **A history of vaccine development**



*Capsular polysaccharide conjugated to carrier proteins. ‡Killed, recombinant B subunit, whole-cell vaccine. §Cholera toxin B combined with enterotoxigenic *Escherichia coli*. ||Now withdrawn.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Haemophilus influenza type B infection (polysaccharide)
Haemophilus influenzae infection (conjugate*)
Cholera (WC-rBC vaccine)‡
Cholera (recombinant toxin B)§
Varicella zoster virus infection — chickenpox or shingles
Lyme disease (OspA protein)‖
Pneumococcal disease (heptavalent pneumococcal conjugate*)
Meningococcal disease (quadrivalent meningococcal conjugates*)
Cholera (whole cell)
Japanese encephalitis (Vero cell culture)
Human papillomavirus infection (bivalent recombinant)
Hepatitis B (yeast or baculovirus recombinant for surface antigen)
Typhoid (live Salmonella enterica subsp. enterica serovar Typhi str. Ty21a)
Japanese encephalitis (inactivated)
Cholera (live attenuated)
Typhoid (Vi capsular polysaccharide)
Acellular pertussis (various)
Hepatitis A (inactivated)
Rotavirus infection (reassortants)
Meningococcal disease (meningococcal conjugate* (group C))
Cold-adapted influenza
Varicella zoster virus infection (live)
Rotavirus infection (attenuated and new reassortants)
Human papillomavirus infection (quadrivalent recombinant)
Pneumococcal disease (13-valent pneumococcal conjugates)

Immunity

Congenital immunity

Species immunity: some microorganisms are pathogenic only for certain animal species

Individual immunity : some people are more resistant than others to diseases

Acquired immunity

Natural

Actively acquired - When the body has already experienced an infection by that pathogen

Passively acquired - Antibodies pass across placenta providing a newborn baby with immunity against disease. Antibodies are also present in breast milk.

Non natural - induced

Actively acquired – ACTIVE IMMUNIZATION.This is by vaccination at a suitable time in the person's life.

Passively acquired – PASSIVE IMMUNIZATION. This is by administrating ready-made antibodies which are able to immediately neutralize the viruses

VACCINES

- **LIVE-VIRUS VACCINES (ATTENUATED VACCINES)**
- **INACTIVATED (NON-LIVING VIRUS) VACCINES**
- **SUBUNIT VACCINES**

Attenuated live-virus vaccines

- Live-virus vaccines use virus mutants that antigenically overlap with wild-type virus but are restricted in some steps of the pathogenesis of the viral disease.
- They were selected empirically by serial passages in animals or cell cultures (usually from a species different from the natural host).
- They multiply in the host and tend to stimulate longer-lasting antibody production, induce a good cell-mediated response, and induce antibody production and (also) resistance at the portal of entry

Killed-virus vaccines

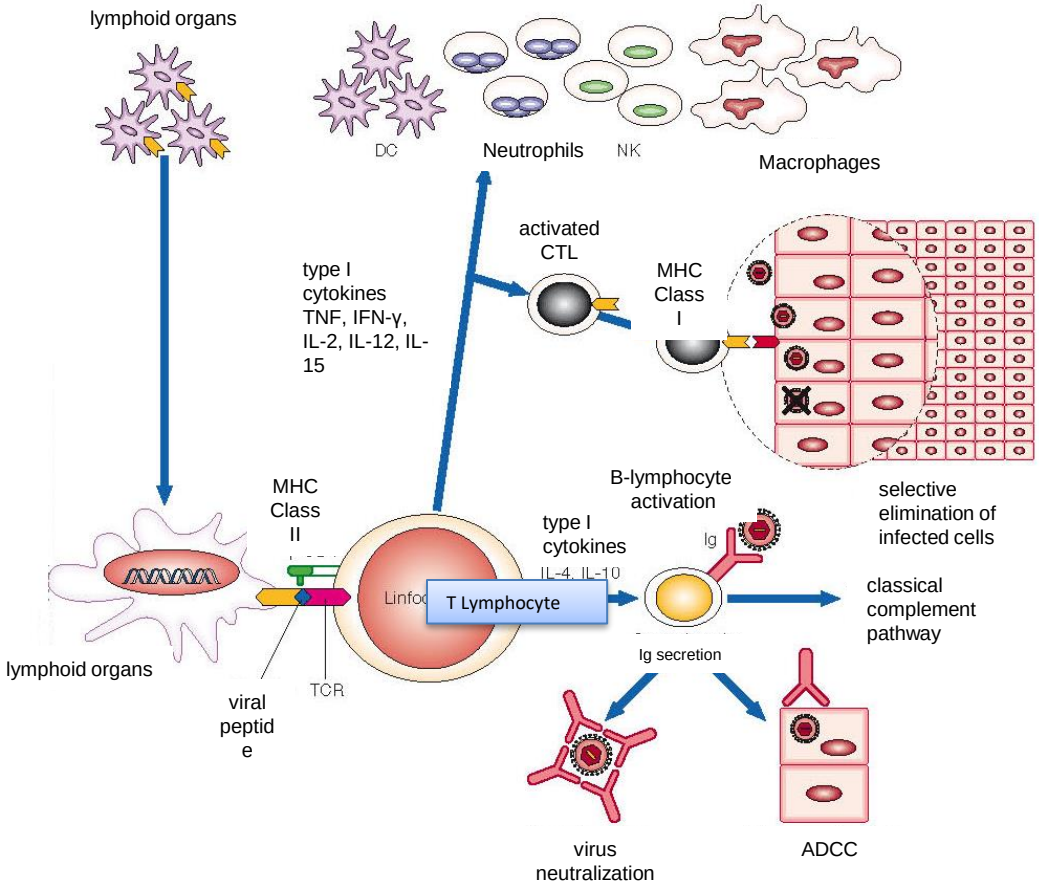
- Inactivated (killed-virus) vaccines are made by inactivating viral infectivity in a way that causes minimal damage to the viral structural proteins; mild formalin is frequently used.
- Extreme care is required in the process of purification to make sure that no residual live virulent virus is still present in the vaccine
- Generally stimulate the development of circulating antibody against the coat proteins of the virus
- The immunity conferred is often brief and must be boosted

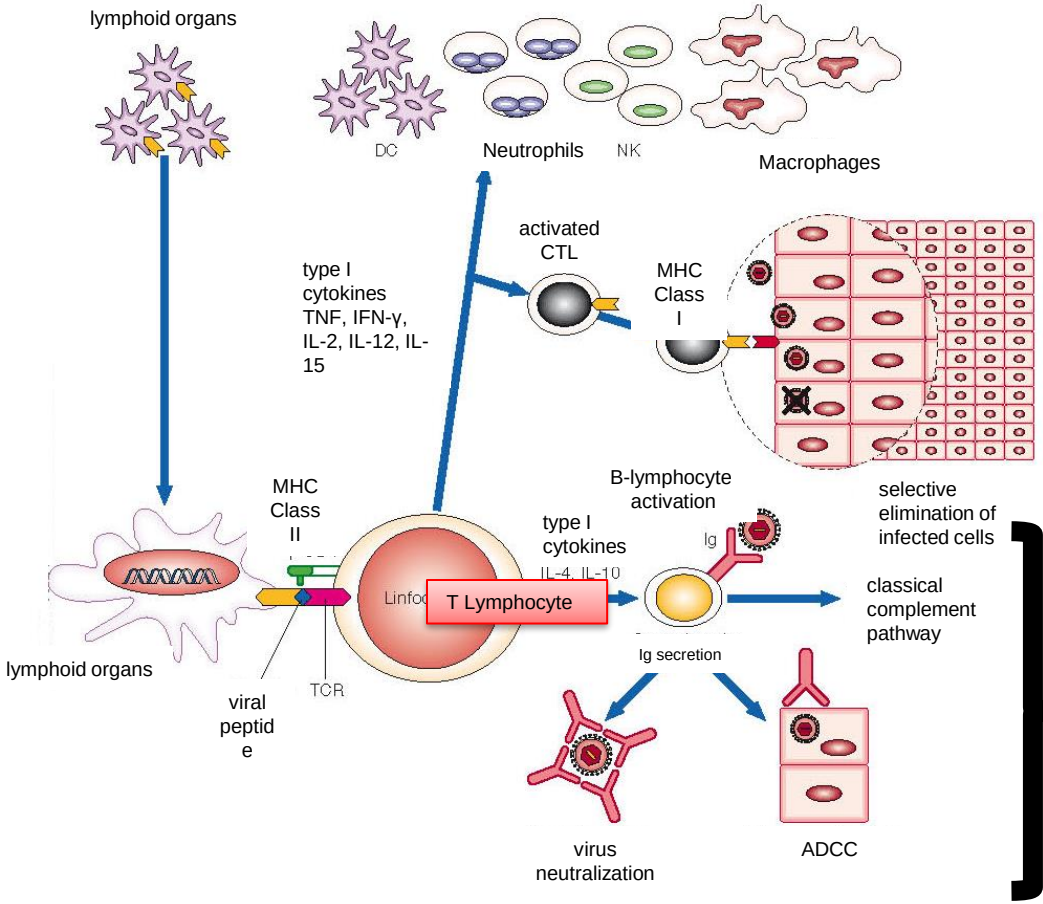
Comparison of characteristics of killed- and live-virus vaccines

Characteristic	Killed vaccine	Live vaccine
Number of doses	Multiple	Single
Need for adjuvant	Yes	No
Duration of immunity	Shorter	Longer
Effectiveness of protection (more closely mimics natural infection)	Lower	Greater
Immunoglobulins produced	IgG	IgA and IgG
Mucosal immunity produced	Poor	Yes
Cell-mediated immunity produced	Poor	Yes
Residual virulent virus in vaccine	Possible	No
Reversion to virulence	No	Possible
Excretion of vaccine virus and transmission to nonimmune contacts	No	Possible
Interference by other viruses in host	No	Possible
Stability at room temperature	High	Low

Subunit vaccines

- Subunit vaccines include only the antigens that best stimulate the immune system
- In some cases, these vaccines are represented by epitopes - the very specific parts of the antigen that antibodies or T cells recognize and bind to (**EPITOPE-BASED VACCINES**)
- Methods of production:
  - grow the virus in the laboratory and then use chemicals to break it apart and gather the important antigens
  - manufacture the antigen molecules from the virus using recombinant DNA technology (**RECOMBINANT VACCINES**)





Attenuated Vaccines

Inactivated Vaccines

Viral Vaccines

Virus	Vaccines Components	Who Should Receive Vaccinations
Polio, inactivated	Trivalent (Salk vaccine)	Children
Attenuated polio	Live (oral polio vaccine, Sabin vaccine)	Children
Measles	Attenuated	Children
Mumps	Attenuated	Children
Rubella	Attenuated	Children
Varicella-zoster	Attenuated	Children
Rotavirus	Human-bovine hybrids Attenuated	Infants
Human papilloma-virus	VLP	Girls aged 9-26 yr
Influenza	Inactivated Attenuated (nasal spray)	Children, adults, especially medical personnel, and the elderly 2-50 yr
Hepatitis B	Subunit (VLP)	Newborns, health care workers, high risk groups (e.g. sexually promiscuous, intravenous drug users)
Hepatitis A	Inactivated	Children, child care workers, travelers to endemic areas, Native Americans and Alaskans
Adenovirus	Attenuated	Military personnel
Yellow fever	Attenuated	Travelers at risk to exposure, military personnel
Rabies	Inactivated	Anyone exposed to virus Preexposure: veterinarians, animal handlers
Smallpox	Live vaccinia virus	Protection from bioterrorism, military
Japanese encephalitis	Inactivated	Travelers at risk to exposure

Future challenges for vaccinologists

Challenges (examples)	Determinants (examples)	Microorganism (Examples)
Climate changes	Incidence, frequency and distribution of several infections	vector-borne diseases, ancient bacteria and viruses
Population growth and urbanization in developing countries	Population density	mosquito-trasmitted diseases, rabies, etc.
Severe infections	No availabilty of curative drugs, variability of the pathogen	HIV, HCV, influenza
Antibiotic resistance	Hospital acquired infections Misuse of antibiotics	Methicillin-resistant staphyloccocus aureus (MRSA) Pseudomonas aeruginosa Clostridium difficile
Emerging infections	The number of emerging viruses is significantly increasing	Norovirus, SARS, MERS

Main features of all antiviral vaccines commercially available (1)

Virus	Type of vaccine	Route of administration	Protocols for administration	Effectiveness	Duration of protection	Possible adverse events
MMR	attenuated	subcutaneous	1st dose between the 13th and 15th month booster dose after the 5th year	93-99%	>30 years	Local: redness, swelling, tenderness General: fever with rash and lymphadenopathy, hypersensitivity, benign thrombocytopenia and neurological manifestations (rare)
HAV	inactivated	intramuscular	2 doses, 6-12 months apart	>97%	>20 years	Fever and headache
Poliovirus	inactivated (IPV) - SALK Attenuated (OPV) SABIN	Intramuscular (IPV)/ oral (OPV)	3 doses in the 1st year of life (3-5-12 months) and a booster at 4 to 6 years of age	>95%	>25 years	No serious adverse reaction Neurological risk abated after switch to killed vaccine
Yellow fever	attenuated	intramuscular	Recommended every 10 years for those travelling in potentially endemic areas	95-98%	>30 years	Fever, headache, myalgias, hypersensitivity reactions
Influenza	inactivated/ attenuated	Intramuscular/ intranasal (LAIV)	Recommended every year for people in high-risk categories	0-90% Possible mismatch between vaccine strains and clinical isolates	1 year	No serious adverse reaction

Legend: MMR:measles-mumps-rubella; HAV: hepatitis A virus; JEV: Japanese encephalitis virus; VZV: varicella-zoster virus; HBV: hepatitis B virus; HPV: human papilloma virus; LAIV: live attenuated influenza vaccine.

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Main features of all antiviral vaccines commercially available (2)

Virus	Type of vaccine	Route of administration	Protocols for administration	Effectiveness	Duration of protection	Possible adverse events
JEV	inactivated	intramuscular	3 doses given on days 0, 7 , 30 before travel to endemic areas	80% after 2 doses 99% after 3 doses	(?)	Fever, headache, nausea, abdominal pain, myalgia, dizziness, neurological complications, skin rashes
VZV	attenuated	subcutaneous	1 dose in children up to 12 years old, 2 doses in older individuals	>90%	(?)	Local: redness, swelling, tenderness General: fever with skin rash
Smallpox	attenuated	subcutaneous	single administration	>95%	3-5 years	Fever, hypersensitivity, cutaneous manifestations, cardiac abnormalities and abnormalities of CNS
HBV	recombinant	intramuscular	3 dosi in the 1st year of life (3-5-12 months)	50-99%	3-5 years	Local:pain General: headache
Rabies virus	inactivated	intramuscular	Pre-exposure: 3 doses given on days 0-7-21 or 28 Post-exposure: 5 doses given on days 0-3-7-14-28 with hyperimmune globulins	100%	>2 years	Headache, dizziness, myalgia, abdominal pain, hypersensitivity, rare neurological complications

Legend: MMR:measles-mumps-rubella; HAV: hepatitis A virus; JEV: Japanese encephalitis virus; VZV: varicella-zoster virus; HBV: hepatitis B virus; HPV: human papilloma virus; LAIV: live attenuated influenza vaccine.

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Main features of all antiviral vaccines commercially available (3)

Virus	Type of vaccine	Route of administration	Protocols for administration	Effectiveness	Duration of protection	Possible adverse events
HPV	recombinant (virus-like-particles)	intramuscular	3 doses beginning at age 9 years, preferably before the onset of sexual activity Not evaluated in males	high but limited to genotypes in the vaccine	(?)	Limited and local, Postmarketing evaluation in progress given the recent introduction
Rotavirus	attenuated	oral	3 doses: the 1st between the 6th and the 15th week of life; 2 at least 4 weeks apart and no later than the eighth month of age	>90%in the prevention of complications requiring hospitalization	(?)	No serious adverse reaction Postmarketing evaluation in progress given the recent introduction Risk of intussusception is strictly controlled given that at the end of 90s a previous vaccine preparation had been withdrawn from the market for this reason

Legend: MMR:measles-mumps-rubella; HAV: hepatitis A virus; JEV: Japanese encephalitis virus; VZV: varicella-zoster virus; HBV: hepatitis B virus; HPV: human papilloma virus; LAIV: live attenuated influenza vaccine.

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Despite the **outstanding success** of vaccination:

- In both developing and industrialized countries, loss of public confidence in a vaccine due to links to adverse events can reduce or even halt immunization activities; the vaccine safety gets more public attention than vaccination effectiveness;
- There is still a great need for new vaccines and these are emerging far more slowly than we would wish;
- Most of our current vaccines were developed by determining the components that consistently stimulated antibody responses in infected patients, often without having a very detailed knowledge of the immune mechanisms required for protection.

Vaccination against infectious diseases: challenges

- Are broadly neutralizing antibodies an absolute necessity?
- We do not know how to generate long-lasting protective antibodies at mucosal surfaces
- There are multiple viral serotypes/genotypes and antigenic variation requires constant updating of vaccine formulations;
- Epidemiological studies have shown that, in addition to disease-specific effects, vaccines against infectious diseases have nonspecific effects on the ability of the immune system to handle other pathogens.
- **No validated immunological correlates of immunity (protective or pathological) do exist**

J Infect Dis. 2016 Apr 15;213(8):1224-8. doi: 10.1093/infdis/jiv456. Epub 2015 Oct 28.

Influence of Statins on Influenza Vaccine Response in Elderly Individuals.

Black S[1], Nicolay U[2], Del Giudice G[3], Rappuoli R[3].

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Abstract

Influenza vaccination strategies have targeted elderly individuals because they are at high risk of disease complications and mortality. Statins are a class of drugs used to treat hypercholesterolemia and are frequently used in the elderly population to reduce the risk of cardiovascular disease. However, statins are also known to have immunomodulatory effects that could impact influenza vaccine response. In a post hoc analysis, we performed a cross-sectional observational study nested within a comparative immunogenicity clinical trial of adjuvanted versus unadjuvanted influenza vaccine in elderly persons to evaluate the influence of statin therapy on the immune response to vaccination. Overall, data on >5000 trial participants were available for analysis. **Comparison of hemagglutination-inhibiting geometric mean titers to influenza A(H1N1), A(H3N2), and B strains revealed that titers were 38% (95% confidence interval [CI], 27%-50%), 67% (95% CI, 54%-80%), and 38% (95% CI, 28%-29%) lower, respectively, in subjects receiving chronic statin therapy, compared with those not receiving chronic statin therapy. This apparent immunosuppressive effect of statins on the vaccine immune response was most dramatic in individuals receiving synthetic statins.** These effects were seen in both the adjuvanted and unadjuvanted vaccine groups in the clinical trial. These results, if confirmed, could have implications both for future clinical trials design, as well as for vaccine use recommendations for elderly individuals.

Vaccination against infectious diseases: challenges

Early-phase human trial is essential even without fully understanding the correlates of protection

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Stringent non human primate model should be used before going in humans

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Further understand the biology of virus infection is needed before going ahead in the vaccine research

Respiratory syncytial virus (RSV)

It is an important pathogen causing, mainly in young children, outbreaks of bronchiolitis every winter, which requires extensive use of hospital paediatric facilities.

A vaccine against this infection would likely be cost-effective, but there is a major challenge.

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The development of vaccines against RSV is hampered by the observation that an experimental vaccine was safe in the acute phase but primed children have more severe disease subsequently when they encountered the live virus because of an immunopathological response

Cytomegalovirus (CMV)

Cytomegalovirus (CMV), damages the hearing and intellectual function of babies born with congenital infection. It also causes disease after transplantation if not prevented by the deployment of antiviral drugs for preemptive therapy or prophylaxis.

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There is evidence for a protective effect of both humoral immunity and cell-mediated immunity, but it is not clear if both of these arms of the immune system must be stimulated in order to control disease.

Dengue virus

It cause up to 100 million cases of dengue annually worldwide. It exists as four distinct serotypes.
Initial infection may be inapparent or cause selflimiting fever. More severe disease, dengue haemorrhagic fever/dengue shock syndrome generally occurs in people who are infected with a second serotype of dengue virus or in infants 6–8 months of age, who experience primary infection in the presence of maternally derived IgG antibodies.

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The major disease caused by dengue virus is immunopathological.

Severe disease is thought to result from immunopathogenic processes involving serotype cross-reactive antibodies and T cells that together induce vasoactive cytokines, causing vascular leakage that leads to shock.

The vaccine may thus appear to be safe in the acute phase, but can we guarantee that waning antibody titres will not facilitate cases of DHF/DSS?

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Vaccination greatly reduces disease, disability, death and inequity worldwide