



Viral Chemotherapy

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Strategies for Controlling Viral Infections

Prevention and control of viral diseases

- 'Prevention is better than cure'
- No effective cures for viral infections
- Hygiene and sanitation: most effective method to prevent enteric infections
- Vector control: to prevent arbovirus transmission
- Chemotherapy and vaccines

Hygiene and Sanitation

- Hand washing and proper sewerage treatment and disposal
- Serious Hep E, polio or gastroenteritis when sewer water contaminates drinking water
- Hand washing with soap is effective in preventing respiratory viruses e.g. Influenza (Flu) and Rhino (cold) viruses



Vector control

- Control of arthropod vectors/use of insecticides
 - *Aedes* mosquitoes transmit Dengue, West Nile viruses
- Elimination of breeding sites
- Avoidance of exposure eg bed nets

Has urbanization contributed to the burst in arboviral transmission?



Quarantine

- Introduced in the fifteenth century to control plague
- Quarantine of ships
- Modern times: air travel
 - People can travel long distances in a shortest possible time
 - Quarantine less effective
 - Incubation time?
 - Vaccination certificates e.g. yellow fever

Change of lifestyle

- Prevention of blood borne viruses
 - Avoidance of needle sharing for IV drug users
 - Practice of safe sex (condoms)
 - E.g. Hepatitis B, C, HIV

- Screening of blood products and blood donors

- Sterilization and disinfection
 - Hospital and dental equipment

Eradication of viral diseases

- Elimination vs eradication
 - Elimination: interruption of transmission within a region
 - Eradication: elimination from the world

- So far only smallpox has been eradicated globally
 - In 1977 last case was reported in Somalia
 - Vaccination and surveillance/containment programs were successful

- Next targets:
 - Measles and polio
 - No animal reservoir, no recurrent infection, few serotypes, effective vaccines

Discuss biological and socio-political/economical features of measles and polio that are similar/different from smallpox and that has affected the global eradication efforts!!!

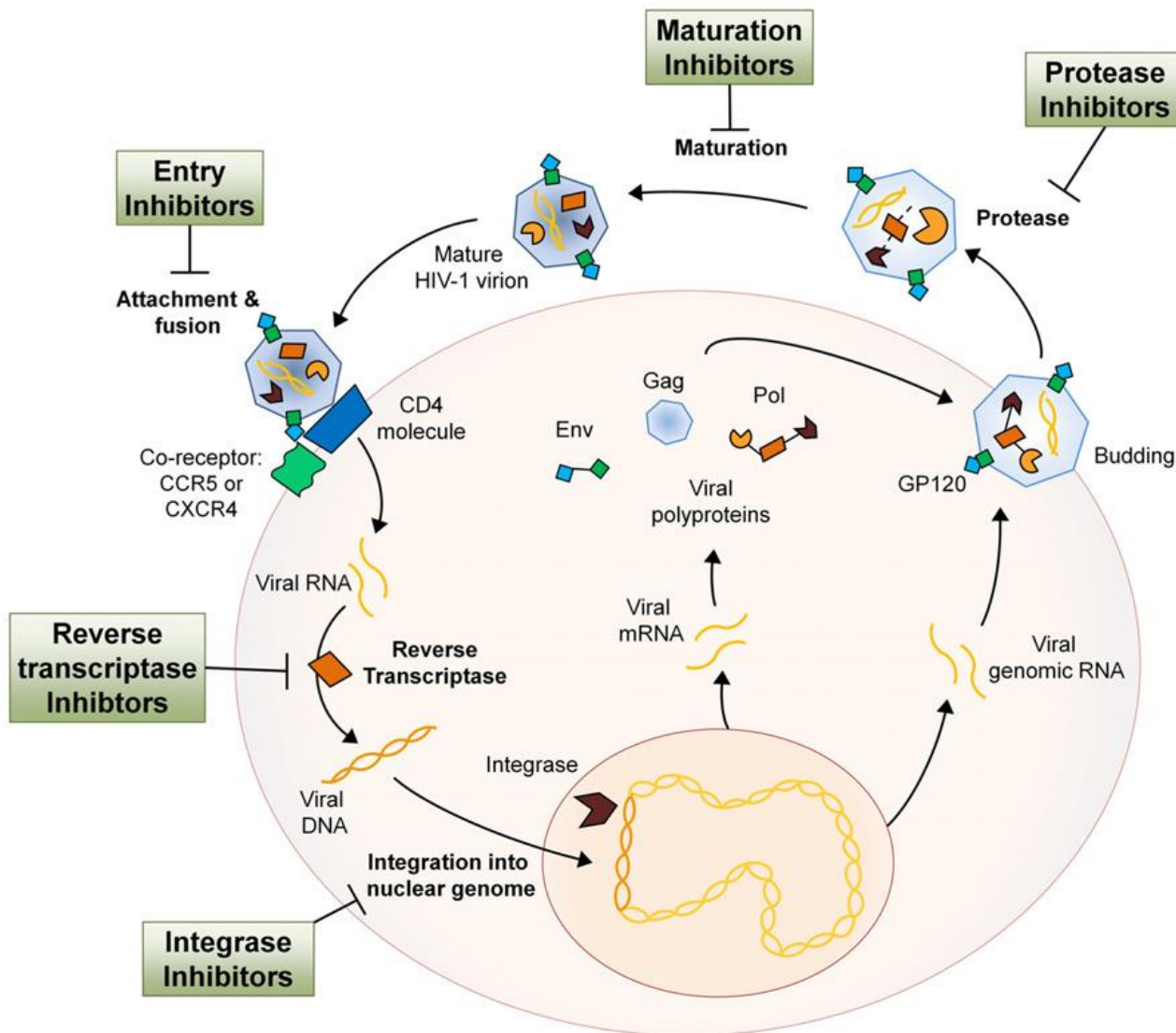


Chemotherapy of viral diseases

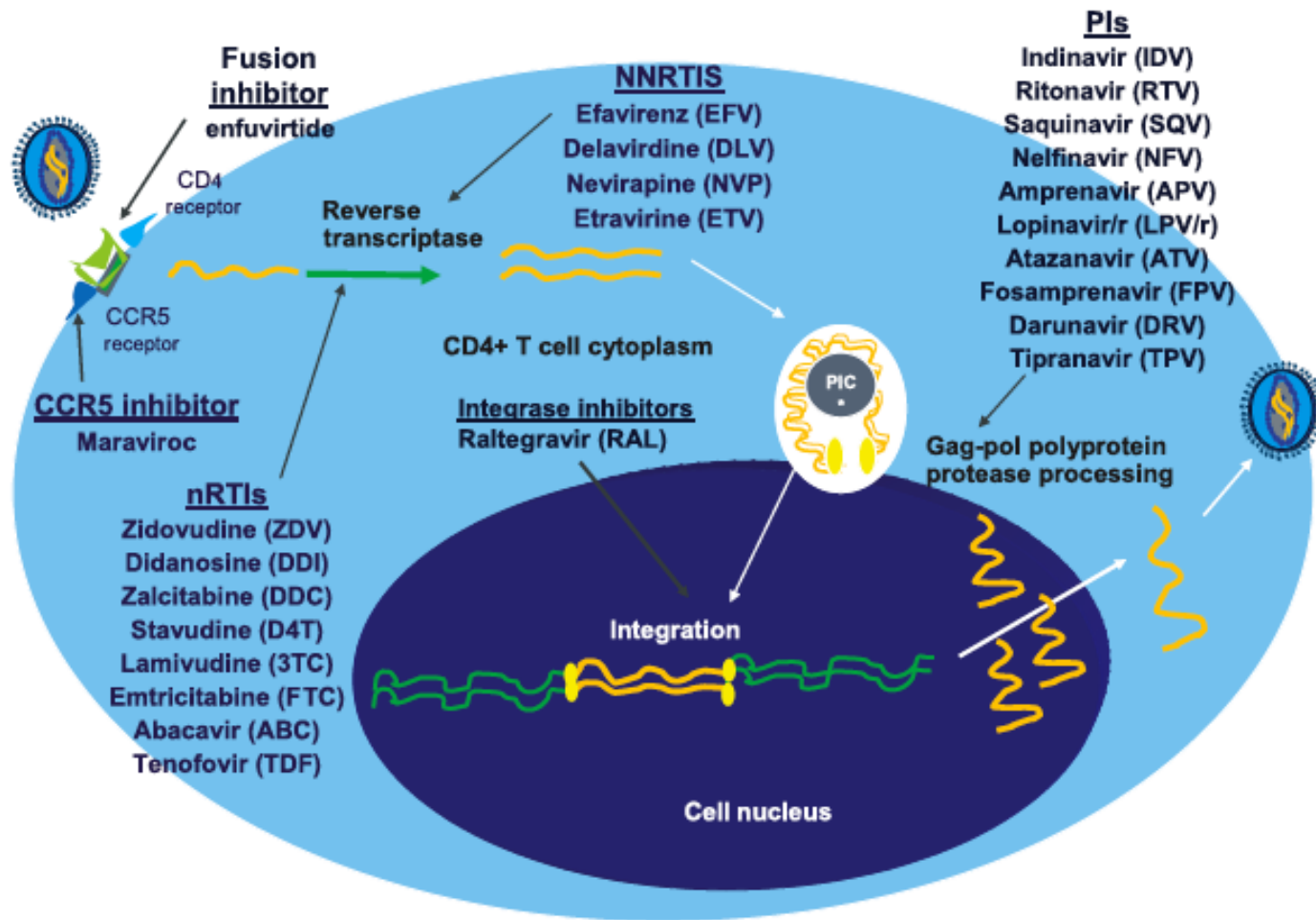
- Numerous antibiotics are available to treat bacterial infections
 - Ineffective against viral infections
 - Only useful for:
 - To prevent or treat superinfections of viral diseases
 - E.g. bacterial pneumonia, complicated influenza
 - To 'play safe' while awaiting laboratory confirmation
 - E.g. meningitis and Pneumonia
- Why there are few effective antivirals?
 - Viruses use host metabolic machinery for replication (obligate intracellular parasites)
- Research in molecular technologies have lead to development of interferons by recombinant DNA technology and inhibitors of viral enzymes. E.g.. Reverse transcriptase inhibitors



Strategies for development of antivirals



1. Attachment
2. Transcription
3. Regulation of transcription
4. Translation of viral mRNA
5. Posttranslational cleavage of viral proteins
6. Integration of viral DNA
7. Replication of proviral DNA
8. Assembly and maturation of virions
9. Virion release



Antiretroviral classes/drugs and their site of activity: nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs); nonnucleoside reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PIs); fusion inhibitor; CCR5 inhibitor; integrase inhibitor; *pre-integration complex (PIC) Clin Microbiol Infect 2009; 15 (Suppl. 1): 69–73

Available HIV antiretroviral agents

□ **Nucleoside reverse transcriptase inhibitors (NRTI)**

- Abacavir/ABC
- Didanosine/ddI
- Lamivudine/3TC
- Emtricitabine/FTC
- Tenofovir/TDF
- Zidovudine/AZT
- *Stavudine/d4T
- *Zalcitabine

□ **Non nucleoside reverse transcriptase inhibitors (NNRTI)**

- Efavirenz/EFV
- Nevirapine/NVP
- Etravirine/ETR
- Rilpivirine/RPV
- *Delavirdine

□ **Protease inhibitors**

- Atazanavir/ATV
- Fosamprenavir/FPV
- Lopinavir/ritonavir LPV/r
- Nelfinavir/NFV
- Ritonavir (small r)
- *Indinavir/IDV
- Saquinavir/SQV
- Darunavir/DRV
- Tipranavir/TPV

□ **Fusion inhibitors**

- Enfuvirtide

□ **CCR5 inhibitors**

- Maraviroc/MVC








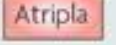









□ **Integrase inhibitors**

- Raltegravir/RAL
- **Elvitegravir/EVG**
- **Dolutegravir**

* Rarely used or discontinued due to adverse effects or pill burden

Investigational drugs: New classes

Class		Drug	Phase	
Entry inhibitors	Attachment inhibitors	TNX-355 (anti-CD4 Ab)	II	
		BMS-488043	I	
	Coreceptor antagonists	CXCR4	AMD-070	I
			AL40-YV	Preclinical
			KRH-2931, -3945, -3140	Preclinical
T-22	Preclinical			
TAK-779	Preclinical			
CCR5	Maraviroc (UK-427,857)	III		
	PRO-140	II		
	AK602	Preclinical		
	TAK-220	Preclinical		
	TAK-652	Preclinical		
SCH-D	On hold			
Integrase inhibitors		MK-0518	Phase III	
		GS-9187	Phase II	
		V-165	Preclinical	
		L-900564	Preclinical	
		Styrylquinolones	Preclinical	
Maturation inhibitors		PA-457	Phase II	
		UK-201844	Preclinical	
Others		D-amino acid peptides	Preclinical	
		RNAse H inhibitors	Preclinical	
		TAT-TAR antagonist	Preclinical	
		Zinc finger inhibitors	Preclinical	

Drug	Class	Pill volume	Total pills per day	Dosing schedule	Combination product	Total pills per day	Dosing schedule	2006 sales [†]	
Tenofovir	NRTI	300 mg		Once daily			Once daily	1,125	
Emtricitabine	NRTI	200 mg		Once daily				Once daily	174
Efavirenz	NNRTI	600 mg		Once daily			-	-	-
Abacavir	NRTI	300 mg		Once daily			Once daily	396	
Lamivudine	NRTI	300 mg		Once daily				Twice daily	478
Zidovudine	NRTI	300 mg		Twice daily				Twice daily	789

*From REF. 2. †Sales in US\$ millions are based on MIDAS sales data, IMS Health April 2007. NNRTI, non-nucleoside transcriptase inhibitor; NRTI, nucleoside transcriptase inhibitor.



Combination antiretroviral therapy (cART)

- cART regiment generally consists of
 - Two NRTIs
 - One of the following
 - NNRTI
 - Protease inhibitor (boosted PI)
 - INSTI (Integrase inhibitor)
 - CCR5 antagonist or fusion inhibitor

- Selection should be individualized based on:
 - Virological and immunological efficacy
 - Toxicity
 - Pill burden
 - Dosing frequency
 - Drug interaction potential
 - Drug resistance
 - Comorbid condition

Preferred HIV Treatment Regimens

- **NNRTI Based regimen**

- **EFV/TDF/FTC**

TDF should be used with caution in patients with renal insufficiency

- **PI Based regimen**

- **ATV/TDF/FTC**

- **DRV/TDF/FTC**

DTG/ABC/3TC should be used in patients who are HLA B*5701 negative

- **INSTI-based regimen**

- **DTG/ABC/3TC**

- **DTG/TDF/FTC**

Ref: DHHS Guidelines,
2013

Alternative HIV Treatment Regimens

□ **NNRTI Based regimen**

- **EFV/ABC/3TC**
- **RPV/TDF/FTC**
- **RPV/ABC/3TC**

□ **PI Based regimen**

- **ATV/ABC/3TC**
- **DRV/ABC/3TC**
- **FPV/ABC/3TC**
- **LPV/ABC/3TC**
- **LPV/TDV/FTC**

□ **INSTI-based regimen**

- **RAL/ABC/3TC**

TDF should be used with caution in patients with renal insufficiency

DTG/ABC/3TC should be used in patients who are HLA B*5701 negative

Ref: DHHS Guidelines,
2013

Challenges to antiviral therapy

- Methods of delivery
 - Routes of administration (pharmacodynamics/pharmacokinetics)
 - e.g. oral, topical, nasal drops, IV or IM
 - Delivery to the brain
 - New delivery methods e.g. use of nanotechnology

- Drug resistance
 - Point mutations (hot spots for particular antivirals)
 - Testing for resistance (genotyping and culture)?
 - Virological failure: measure viral load during the course of treatment
 - Immunological failure: measure CD4 counts during the course of treatment

Complications of HIV Therapy

- **Lipodystrophy**
- bleeding
- Bone marrow suppression
- **Cardiovascular disease**
- CNS disease
- Diabetes/insulin resistance
- Dyslipidemia
- GI effects
- **Hepatic toxicity**
- Hypersensitive reactions
- Lactic acidosis
- Myopathy
- **Nephrotoxicity**
- **Peripheral neuropathy**
- Rashes

Common HIV co-morbid conditions

□ Haematological complications

- Thrombocytopenia
- Anaemia
- Neutropenia
- Eosinophilia

□ Oncological complications

- Kaposi's sarcoma
- Non-hodgkin's lymphoma
- Primary CNS lymphoma
- Anal cancer
- Cervical cancer

□ Endocrine complications

- Disorders of adrenal function
- Hypogonadism
- Thyroid disease
- Pancreatitis
- Hyperglycemia
- Hypoglycemia
- Ovarian complications
- Bone disease

□ Gastrointestinal complications

- Nausea and vomiting
- Anorexia
- Diarrhea
- Oral ulcers

□ Renal complications

- Nephropathy (HIVAN)

□ Cardiac complications

- Cardiomyopathy
- Pericarditis/effusion
- Endocarditis

□ Pulmonary Complications

- Pulmonary hypertension
- Pneumonitis

Common HIV co-morbid conditions

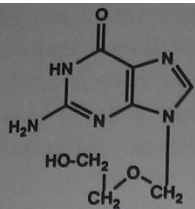
- Musculoskeletal complications
 - Arthropathy
 - Myopathy

- Neurological complications
 - Distal sensory neuropathy
 - HIV associated dementia
 - HIV encephalopathy

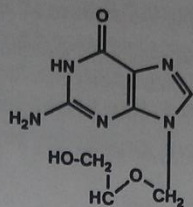
- Psychiatric complications
 - Depression
 - Mania
 - Insomnia

- Dermatological complications
 - Skin infections
 - Viral
 - Bacteria;
 - Fungal

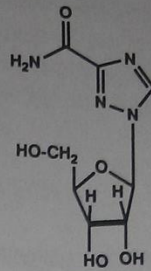
Antiviral chemotherapeutic agents



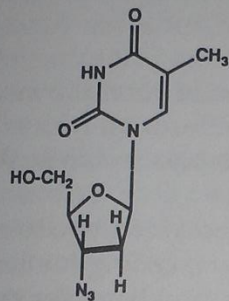
Acycloguanosine (Acyclovir)



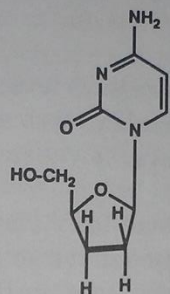
Ganciclovir



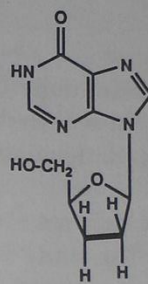
Ribavirin



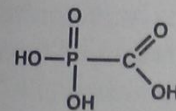
Zidovudine (AZT)



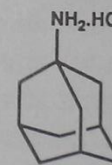
Dideoxycytidine (ddC)



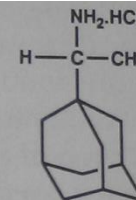
Dideoxyinosine (ddI)



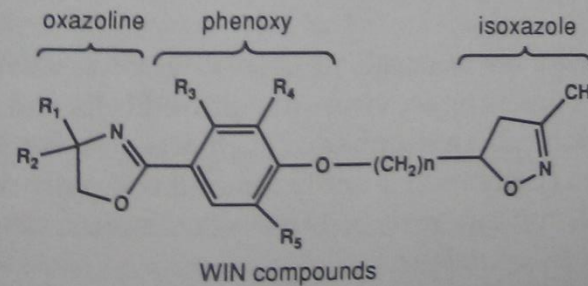
Foscarnet (PFA)



1-Adamantanamine hydrochloride (Amantadine)



Rimantadine



WIN compounds

Antiviral drugs

□ 1. Interferons

- Discovered in 1957
- Ideal antivirals
 - Natural
 - Broad spectrum
- 1980: Human IFN- α was cloned and expressed in *E coli*
 - INF- β and INF- γ have been cloned and expressed in prokaryotic and eukaryotic cells
- Not effective by mouth, injected
- Toxic side effects (severe fatigue)
- Hepatitis C and genital warts are some of the viral diseases treated with interferons

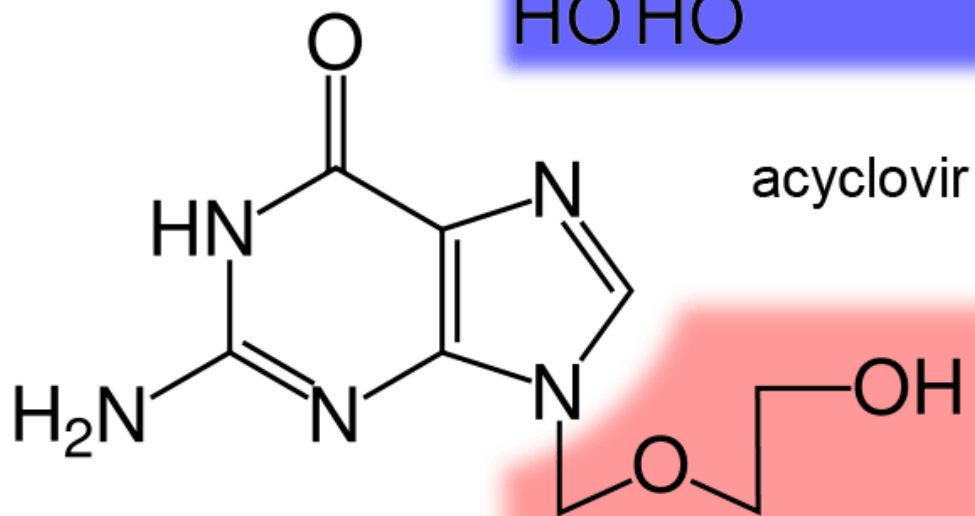
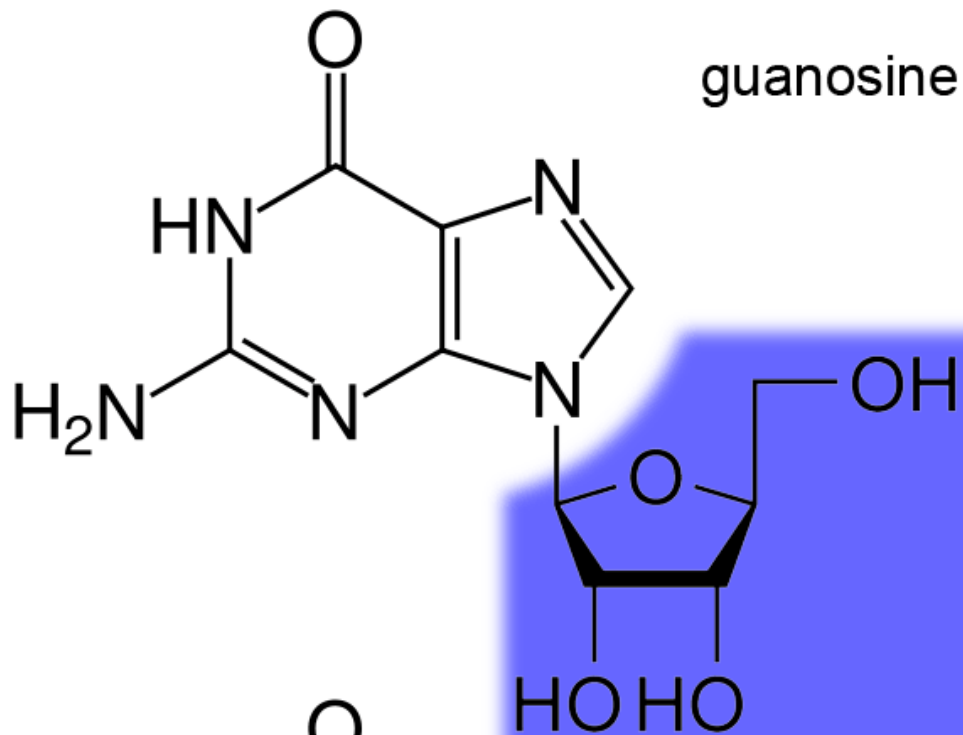


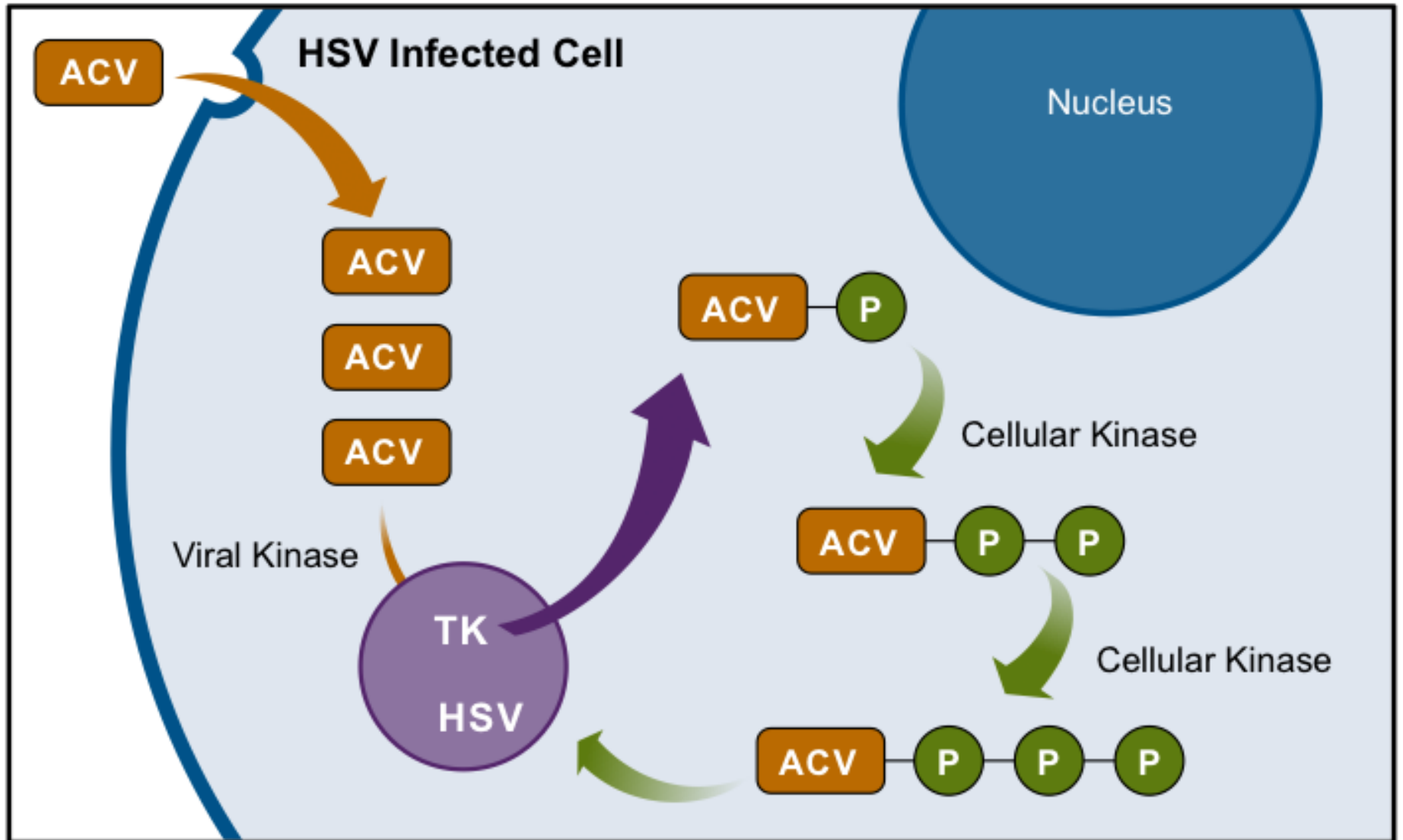
Inhibitors of viral DNA polymerase

- Nucleoside analogs



- 1. Acycloguanosine (Acyclovir) and homologs
 - Guanosine derivatives with an acidic side chain
 - Herpesvirus encoded enzyme, thymidine kinase, phosphorylates the drug to ACG-P and a cellular GMP kinase completes the phosphorylation to ACG-PPP
 - ACG-PPP inhibits herpesvirus DNA polymerase α via chain elongation termination
 - Non-toxic to uninfected cells
 - Can be given orally or by IV or topically

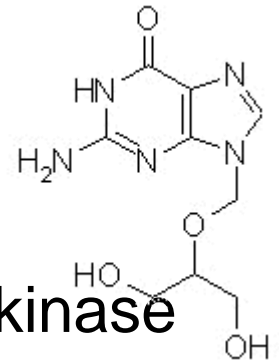




Inhibitors of viral DNA polymerase

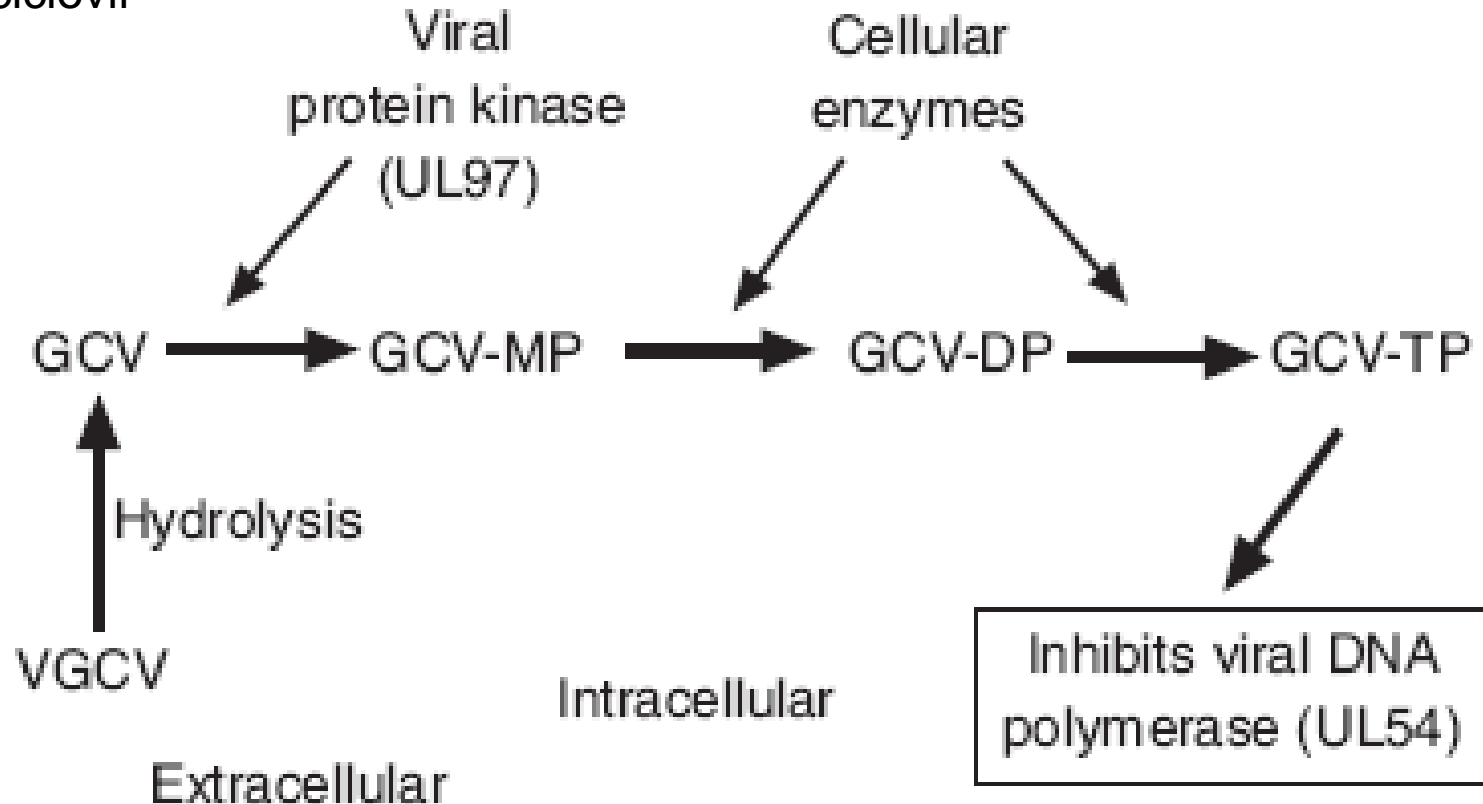
□ 2. Ganciclovir

- A derivative of acyclovir (DHPG)
- Effective against CMV infection
- Mechanism is similar to acyclovir, a CMV kinase phosphorylates DHPG to a monophosphate and then cellular kinases to a triphosphate which inhibits the DNA polymerase elongation by chain termination
- Not effective by mouth, given IV
- Very toxic, produces neutropenia and thrombocytopenia



Inhibitors of viral DNA polymerase

Ganciclovir

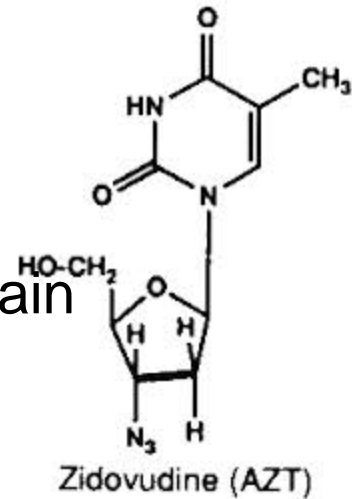


Inhibitors of viral DNA polymerase

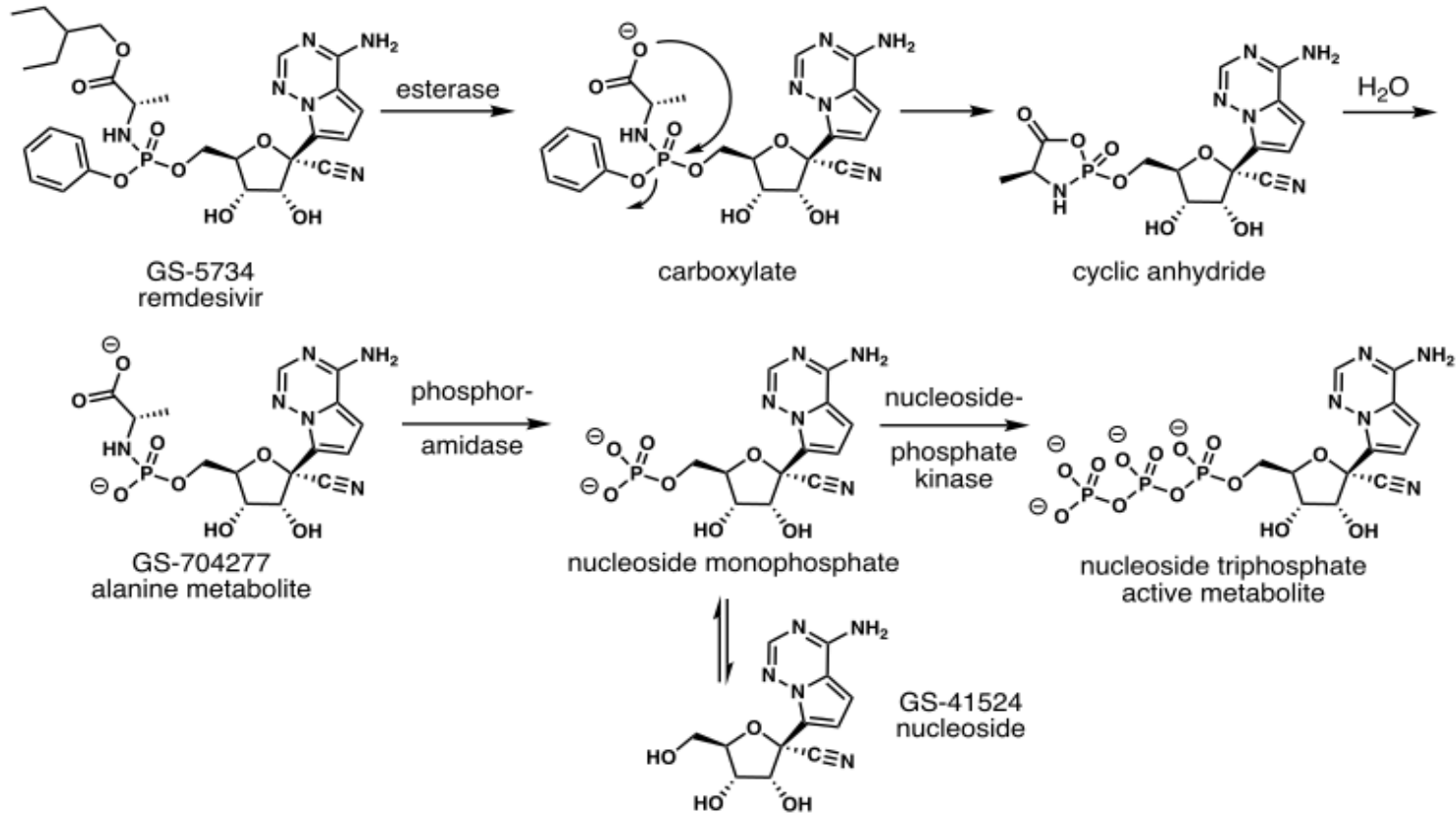
- 3. Ribavirin
 - Also a nucleoside analog
 - Inhibit DNA and RNA viruses
 - Toxic, causes anemia
 - Used to treat RSV infections

Inhibitors of reverse transcriptase

- 1. Zidovudine and homologs
 - Phosphorylated to AZT-PPP by cellular enzymes
 - AZT-PPP is preferred by RTase
 - AZT-PPP is incorporated in the growing HIV DNA chain leading to premature termination
 - Does not eliminate HIV in latently infected cells
 - Resting T cells, monocytes/macrophages/microglia (reservoirs)
 - Drug toxicity
 - Useful in preventing mother-to-child HIV infection
 - Resistance is the major challenge
 - Mutants rise over time
 - Following withdrawal susceptible quasispecies repopulate
 - Drug resistance can be mitigated by combinational therapy, alternating courses of drugs



2. Remdesivir



As an adenosine nucleotide triphosphate analogue, the active metabolite of remdesivir interferes with the action of viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production

Ion channel blockers

- Amantadine
 - Works against influenza A virus
 - Targets protein M2 envelop protein
 - Ion channel that reduces pH of the acidified endosome
 - Important for uncoating and assembly of virions and transport of viruses via the trans golgi network
 - Blocks the ion channel and raised the pH of the endosome
 - Prevents Hemagglutinin conformation change required for fusion of envelop with the endosome
 - Disturbs the ionic environment which prevents conformational change of hemagglutinin required for incorporation into the envelop of budding virions

Neuraminidase Inhibitors (NI)

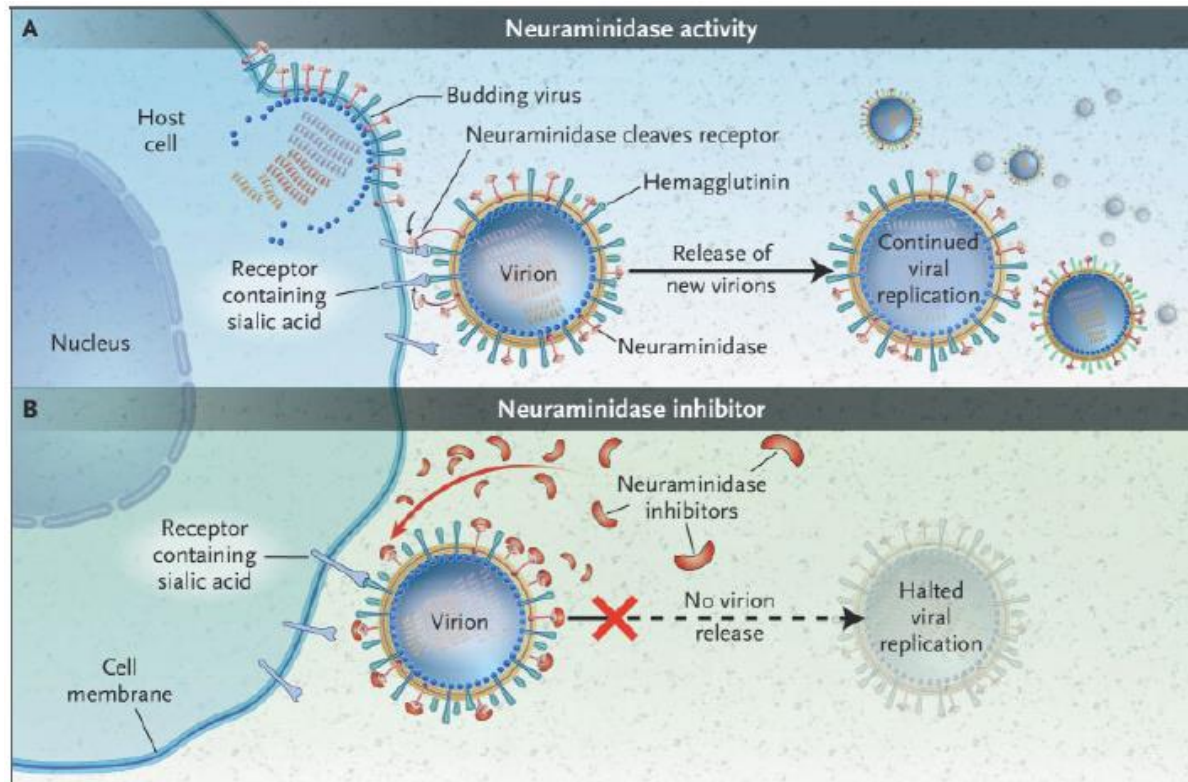


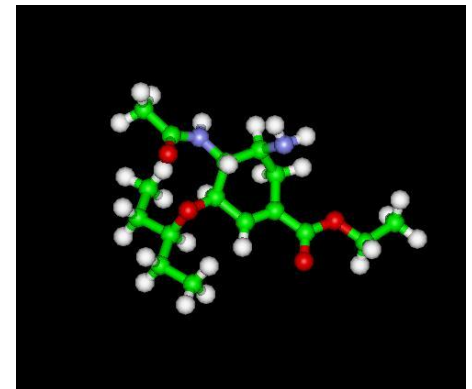
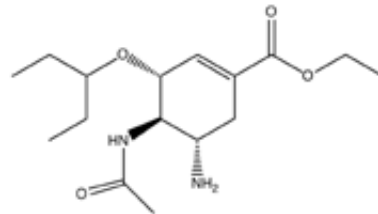
Figure 1. Mechanism of Action of Neuraminidase Inhibitors.

Panel A shows the action of neuraminidase in the continued replication of virions in influenza infection. The replication is blocked by neuraminidase inhibitors (Panel B), which prevent virions from being released from the surface of infected cells.

Neuraminidase Inhibitors (NI)

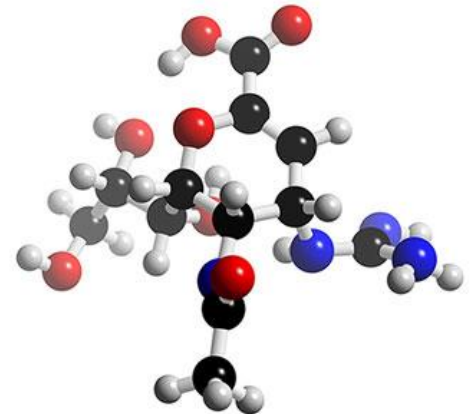
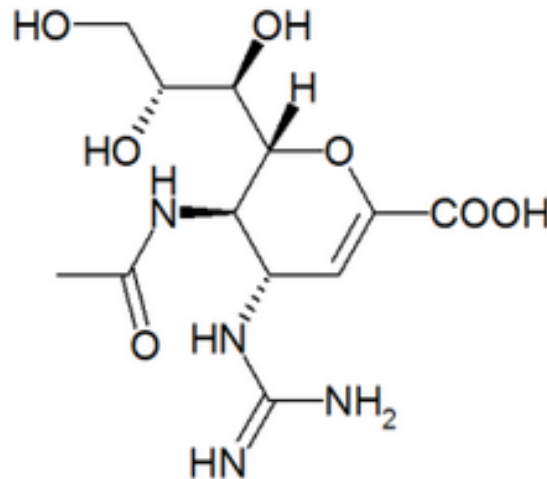
■ Oseltamivir (Tamiflu®, Roche)

- ❑ Administered orally as a prodrug (oseltamivir carboxylate; 75mg pill)
- ❑ Systemically distributed to all potential sites of infection
- ❑ Significantly reduces illness duration and symptom severity
- ❑ Decrease the rate of influenza-associated complications
- ❑ Greater benefits when treatments are initiated early (<12 hours)
- ❑ Works well for post-exposure prophylaxis (PEP) for close contacts
- ❑ Well tolerated and low levels of resistance



Neuraminidase Inhibitors (NI)

- Zanamivir (Relenza®, Glaxo-Smith-Kline)
 - Discovered in 1989 by Biota Holdings (Australia)
 - Administered by inhalation (2 doses/day) via disk inhaler
 - Deposited in respiratory tract
 - Reduces illness duration and symptom severity
 - Decrease the rate of influenza-associated complications
 - Well tolerated and low levels of resistance



Other antiviral targets

- Blocking attachment or uncoating
 - CCR5 blockers
 - HIV
 - Maraviroc
- Inhibitors of viral proteases
 - Proteases are required to cleave viral proteins
- Virus specific-oligonucleotides
 - Antisense oligonucleotides complementary to viral mRNA
 - Can hybridize to viral mRNA
 - Prevent translation and make RNA susceptible to RNase H degradation
 - Hybridization to viral cDNA
 - May block replication
- Inhibitors of regulatory proteins
 - E.g. agents that could inhibit HIV *tat* that could bind to the TAR region of DNA may inhibit HIV replication
 - Some of these agents are undergoing clinical trials



Viral Vaccines

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Medical Microbiology

[Two major contributors to public health in past 100 years]

⇒ Sanitation

⇒ Vaccination

Together have drastically reduced deaths from infectious disease

Acquisition of Passive and Active Immunity

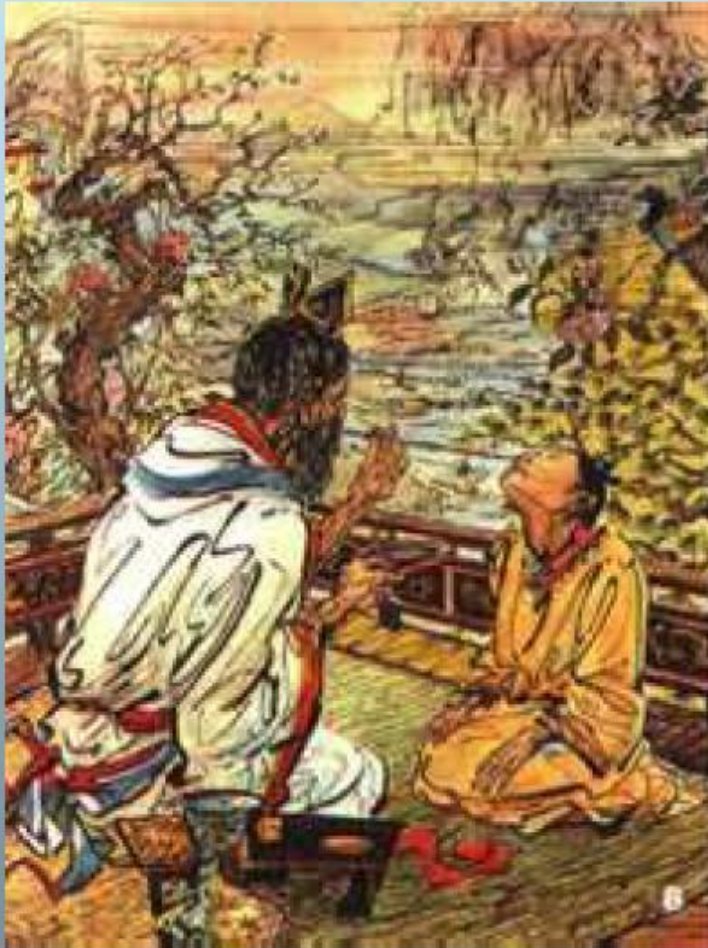
□ Passive Immunity:

- Natural maternal antibody (IgG)
- Immunoglobulin
 - Antitoxin or anti-venom

□ Active Immunity

- Natural infection
- Vaccine (artificial immunization)
 - Live attenuated organisms (mostly administered orally)
 - Inactivated /killed organisms (Mostly administered IV or IM)
 - Whole killed organism
 - Purified microbial macromolecules/inactivated Toxoid /Capsule
 - Cloned microbial antigens (DNA vaccines, alone or in vectors)
 - Multivalent complexes

Beginnings of Vaccinology



- “Variolation”
 - Ancient Chinese practice introduced as early as 10th century
 - Inoculate pus from smallpox patients to prevent severe smallpox
 - Insert lesion material under skin or powdered scabs into nose
 - Common practice 14-17th centuries in China, India, Turkey
 - Introduced into Europe in early 18th century
 - Noted by Lady Mary Wortley Montagu, poet & wife of British ambassador to Turkey
 - Vaccination first spread to Turkey
 - Started vaccinating in England during smallpox epidemic (18th century)

Edward Jenner: From *Variolation* to *Vaccination*

- Early 1700s
 - Milkmaids protected against smallpox by prior infection with cowpox
 - Farmer Benjamin Justy inoculated family with cowpox pus to prevent smallpox
- 1796
 - First human, scientific investigation of smallpox prevention (Jenner)
 - Observation that patients exposed to mild disease “cowpox” did not develop smallpox
 - Lesions produced by cowpox much smaller than smallpox
 - Infected young boy with material from cowpox lesion
 - After recovery, injected pus from smallpox lesion into skin
 - Result: boy did not develop smallpox



- 19th century
 - Cowpox vaccination became worldwide practice, esp. in Europe and North America

[Early Vaccines]

- Important concepts in vaccinology, immunology
 - *Louis Pasteur* – immuno-prophylaxis, attenuation
 - *Robert Koch* – pure bacterial culture methodology, hypersensitivity, discovery of cholera & tubercle bacilli
 - *Emil von Behring* – antibodies & immunotherapy
 - *Paul Ehrlich* – specific ligand-receptor binding; chemotherapy (first syphilis drug), measurement of antibodies
- First useful vaccines
 - Smallpox & rabies
 - Killed and/or attenuated typhoid, shigella, cholera
 - Plague, diphtheria, tetanus, pertussis, tuberculosis

[Types of Vaccines]

- Inactivated vaccines
 - Prepared through chemical or heat inactivation of bacteria, bacterial toxins, viruses
 - May be further purified into essential components
 - Inactivated toxins (toxoid)
 - Capsule or protein subunits
 - Polysaccharides may require conjugation to protein carriers for improved immunogenicity
 - Require administration with adjuvant to boost immunogenicity
 - *Adjuvant*: any substance that enhances the immune response to an antigen when administered as a mixture
 - Usually alum (aluminum hydroxide)
 - Other adjuvants under development
 - Generally safe except in people with allergies to vaccine components

[Types of Vaccines]

- Live, attenuated vaccines
 - Prepared with organisms limited in ability to cause disease (attenuated or avirulent)
 - Methods of attenuation
 - Viruses
 - Temperature-sensitive strains – adapted to grow poorly @ 37°C
 - Host-range mutants – do not replicate in human cells
 - Sensitive to immune control
 - Replicate at benign site of introduction, but do not disseminate, bind or replicate in target tissue affected by diseases
 - Bacteria
 - Genetically altered to produce limited infection (*Salmonella typhi* Ty21a)
 - Attenuated strains of related species that are less pathogenic in humans than natural host (eg. BCG: *Mycobacterium bovis*)

Advantages and Disadvantages of Live vs. Inactivated Vaccines

Property	Live	Inactivated
Route	Natural or injection	Injection
Dose/Cost	Low	Higher
No. Doses	Single	Multiple
Adjuvant	No	Yes
Duration of immunity	Long-term	Short-term
Antibody response	IgM, IgG, IgA	IgM, IgG
CMI response	Good	Poor
Heat labile	Yes	Variable
Interference	Occasional	None
Side effects	Occasional, mild	Occasional
Reversion to virulence	Rare but does occur	None

Current Viral Vaccines

Virus	Vaccine Components	Target Population
Polio	Inactivated (IPV, Salk) Attenuated (oral, Sabin)	Children
Measles	Attenuated	Children
Mumps	Attenuated	Children
Rubella	Attenuated	Children
Varicella-zoster	Attenuated	Children
Influenza	Inactivated	Adults (esp. medical personnel, elderly)
Hepatitis B	Subunit	Newborns, medical personnel, high-risk groups
Hepatitis A	Inactivated	Children, high-risk groups
Adenovirus	Attenuated	Military personnel
Yellow fever	Attenuated	Travelers, military personnel

[Current Viral Vaccines]

Virus	Vaccine Components	Target Population
Rabies	Inactivated	Virus-exposed; high risk
Rotavirus	Rhesus/bovine/human hybrid	In development Under trial in Zambia
Smallpox	Live vaccinia virus	Military, biodefense
Japanese encephalitis	Inactivated	Travelers
Eastern, Western, Russian spring-summer encephalitis viruses	Inactivated	Military

Immunization schedule for infants recommended by the WHO Expanded Programme on Immunization (EPI) for developing countries

Vaccine	Age				
	Birth	6 Weeks	10 Weeks	14 Weeks	9 months
BCG	X				
Oral polio	X	X	X	X	
Hepatitis B Hi prev	X	X			
Lo prev		X	X	X	
<i>Hemophilus influenzae</i> type b		X	X	X	
Yellow fever					X
Measles					X

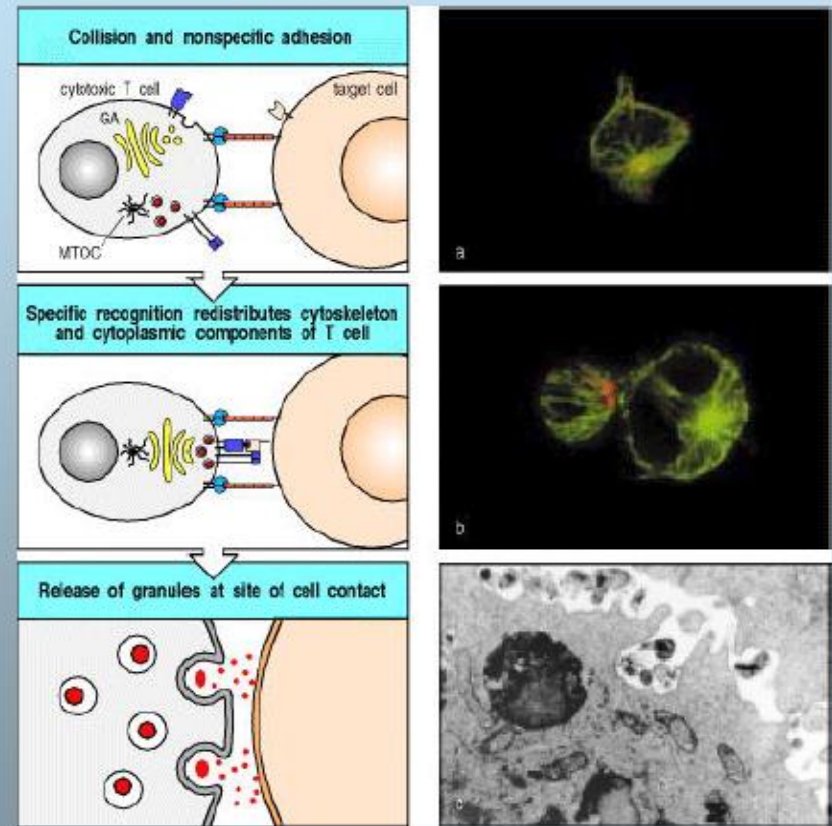
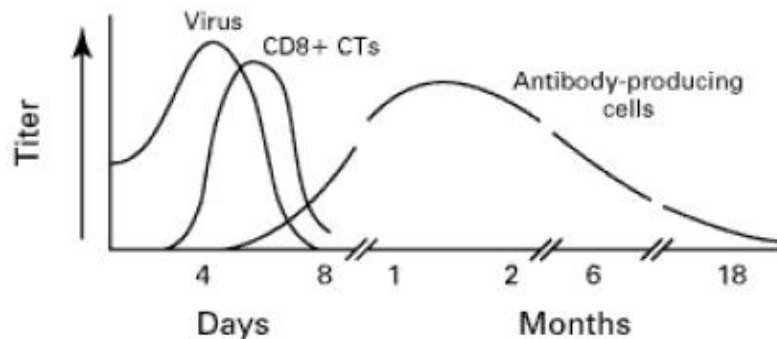
Core information for the development of immunization policy, 2002 update, Vaccines and Biologicals, World Health Organization.

Mechanisms of immunity induced by *vaccination*

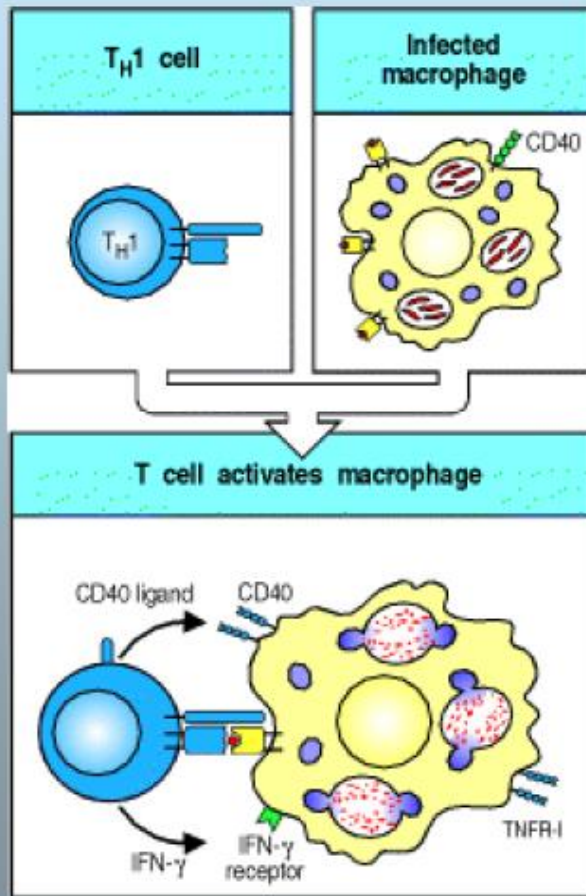
- Antibody-mediated mechanisms
 - Prevention or limitation of initial infection
 - Example: virus neutralization
 - Prevention of spread of infection by viremia or bacteremia
 - Killing of infected cells
 - antibody-dependent cellular cytotoxicity, or
 - complement-mediated lysis
- Production of antibody & immune memory requires priming of B cells & CD4⁺ type 1 T helper cells (Th1)
 - Class switching requires the cooperation of Th1 & Th2 cells
 - Th1: switching to IgG2a
 - Opsonization, complement activation
 - Th2: switching to IgE, IgG1
 - IgE: parasitic defense, immediate hypersensitivity reaction
 - Successful vaccine should induce memory response for *all* relevant cell types

Mechanisms of immunity induced by *vaccination*

- Cell-mediated immune mechanisms
 - Destruction of virus-infected cells by CD8+ cytotoxic cells
 - May emerge earlier during infection than antibodies
 - Target cells often killed by apoptotic mechanism
 - Also secrete cytokines with anti-viral and macrophage-activating activities (eg. $\text{IFN}\gamma$)



Mechanisms of immunity induced by *vaccination*



- Cell-mediated immune mechanisms
 - Macrophages activated by antigen-stimulated CD4+ type 1 helper T cells (Th1)
 - Increase expression of CD40 & TNF receptors
 - Secrete TNF- α
 - Enhance antimicrobial action through production of nitric oxide (NO) and oxygen radicals (O₂[•])
 - Destruction of intracellular bacteria by activated macrophages

[Polio vaccine]

Sabin polio vaccine:

A live, attenuated poliovirus vaccine

Salk polio vaccine:

An inactivated poliovirus vaccine

[Polio Eradication Campaign]

- Vaccine-associated paralytic poliomyelitis
 - Associated with transmission of vaccine strain to immunocompromised contacts
 - Risks/benefits of OPV vs. IPV
 - OPV (Sabin) – live vaccine, administered orally, single dose
 - Superior ability to induce intestinal/mucosal immunity (IgA) as well as serum IgG & to prevent spread among close contacts
 - Vaccine of choice in areas where wild poliovirus still present
 - Risk of vaccine-virus induced polio disease
 - IPV (Salk) – inactivated poliovirus vaccine, administered parenterally, multiple doses (3)
 - Effective in inducing circulating antibody titers (IgG) but not mucosal immunity
 - No risk of transmission to contacts
 - Routine vaccination in non-endemic areas (eg. US)

Vaccines

- Inactivated Polio Vaccine (IPV) in 1955, Salk Vaccine
 - Contains all three serotypes
 - Inactivated with formaldehyde
 - Administered IV or IM

- Advantages:
 - Protection from paralysis with neutralizing Ab (IgG)
 - No risk of vaccine-associated paralytic poliomyelitis (VAPP)

- Disadvantages:
 - Less GI mucosal immunity
 - Recipients of IPV are readily infected with wild-type Polio virus
 - Duration of immunity not known

Vaccines

- Oral Polio Vaccine (OPV) 1963, Sabin Vaccine
 - Contains all three live-attenuated serotypes
- Advantages:
 - Life-long immunity
 - Excellent GI mucosal immunity (IgG and IgA)
 - Prevent wild-type Poliovirus transmission (Herd immunity)
- Disadvantages:
 - May be transmitted via fecal-oral to close contacts causing VAPP
 - Vaccine virus replicate in intestine mucosa and local draining lymph nodes
 - shed in feces up to six weeks post immunization
 - Risk to the immuno-compromised
 - Does not grow/Disseminate well to the CNS

When should we stop OPV?

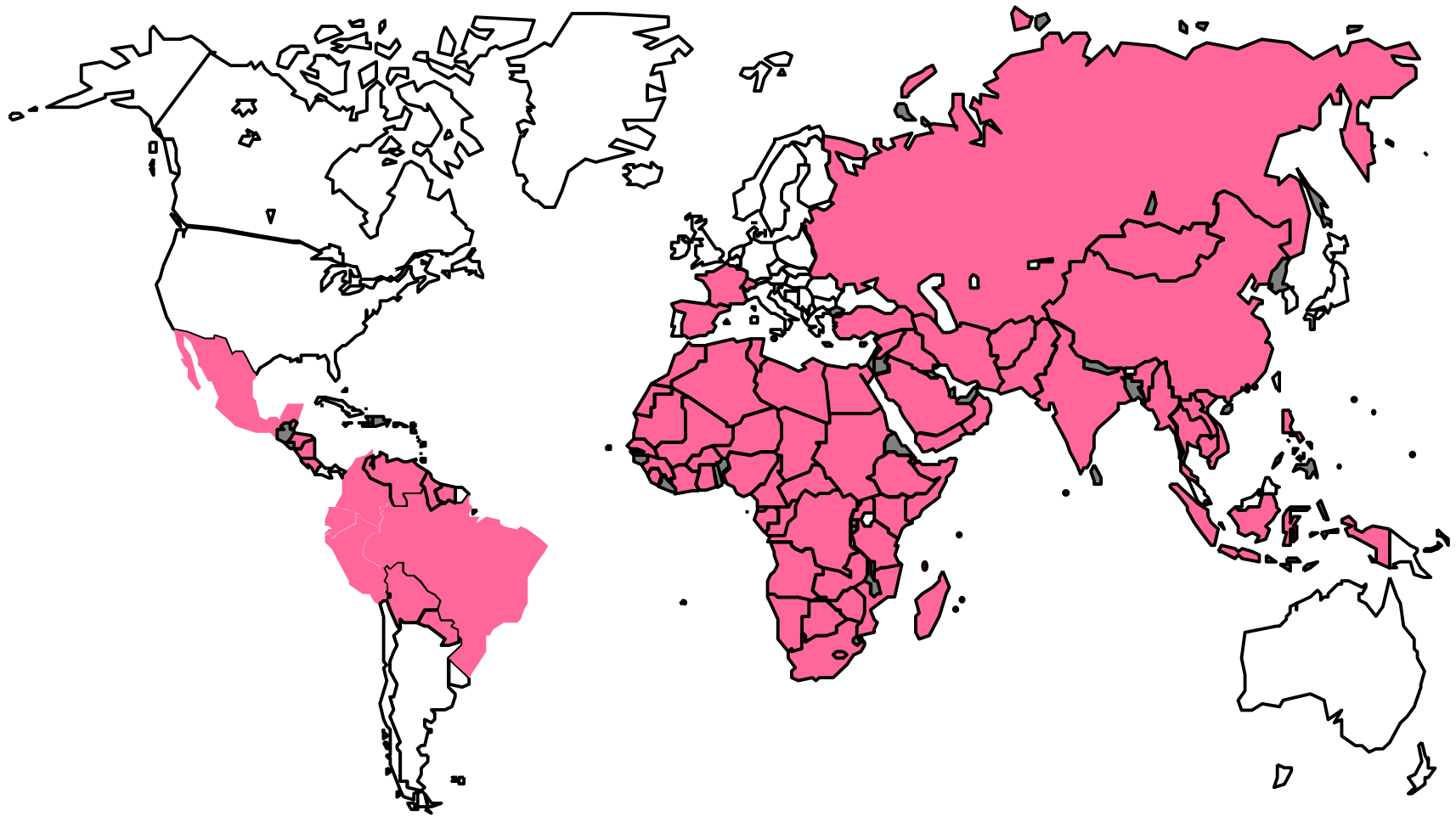
Should we continue indefinitely with IPV or stop all immunization after polio is considered “eradicated” (*a la* smallpox)?

Bioterrorism issues?

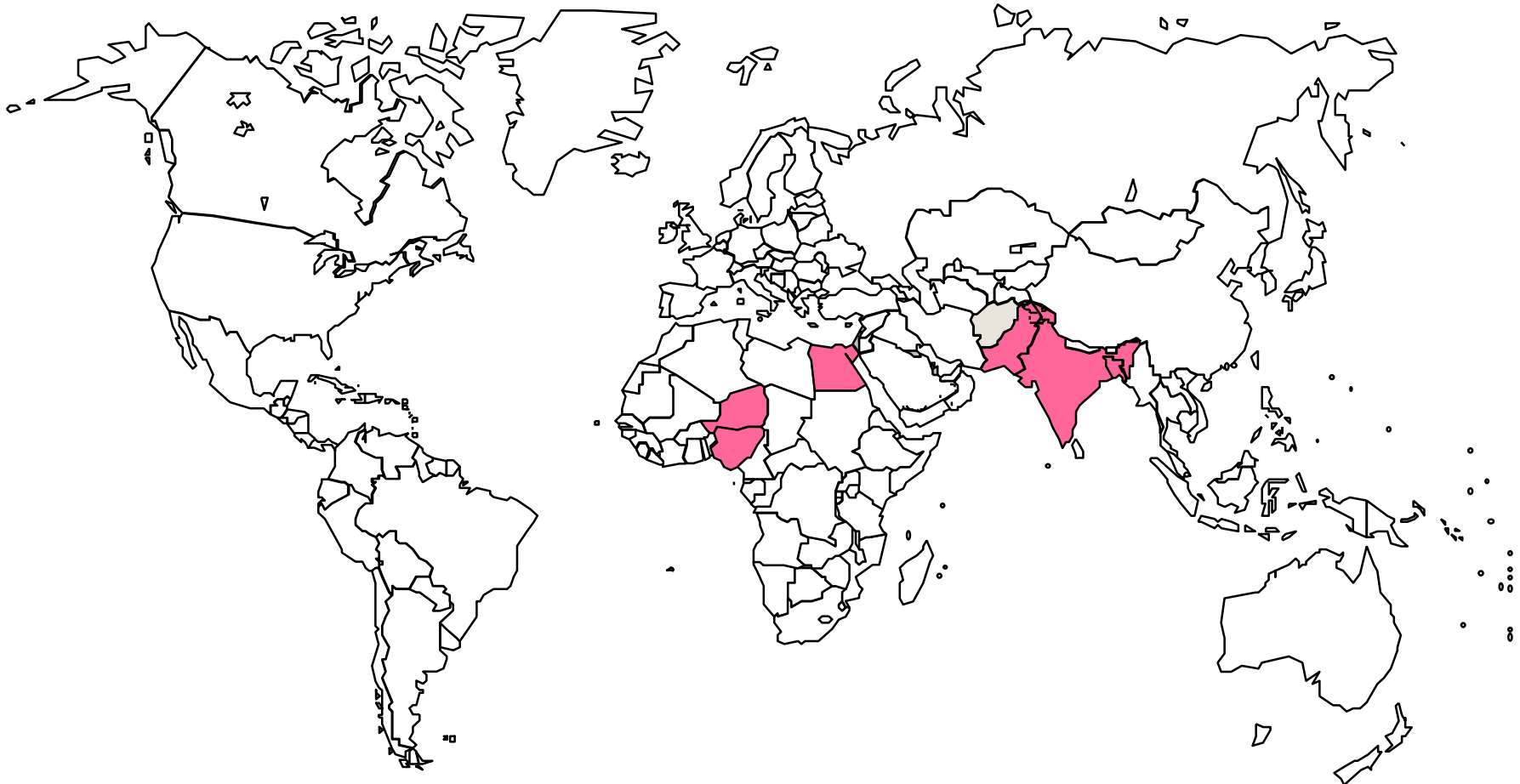


Luis Tenorio – the last polio case in the Western Hemisphere

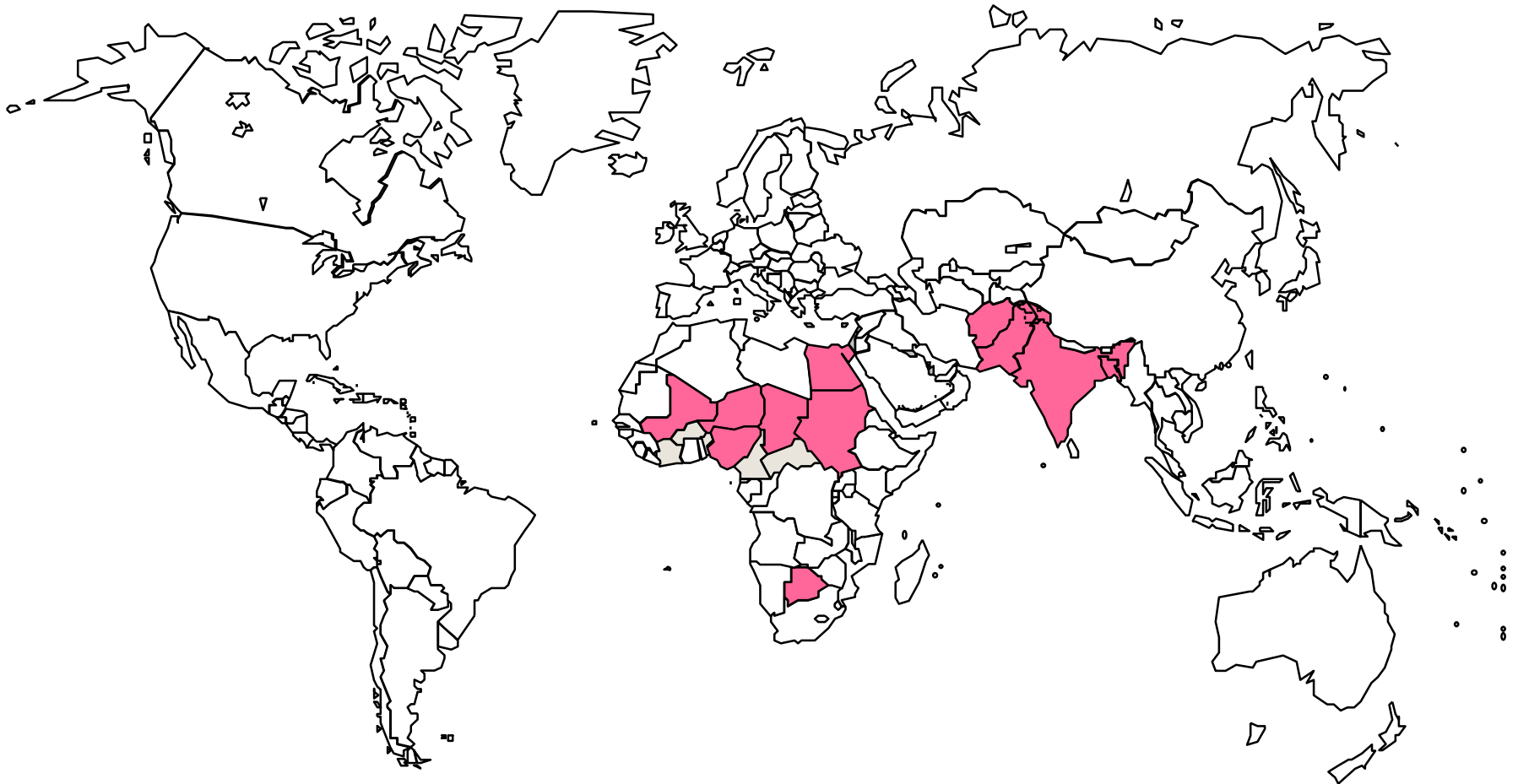
Wild Poliovirus 1988



Wild Poliovirus 2003



Wild Poliovirus 2004



Polio as of 2014

- The number of worldwide polio cases has fallen from an estimated 350,000 in 1988 to 407 in 2013—a decline of more than 99% in reported cases.
- Four regions of the world are certified polio free—the Americas, Europe, South East Asia and the Western Pacific. Only three polio-endemic countries (countries that have never interrupted the transmission of wild poliovirus) remain—**Afghanistan, Nigeria, and Pakistan**.
- January 13, 2014 marked three years since a child was paralyzed by wild poliovirus in **India**.
- The country was once considered the most complex challenge to achieving global polio eradication.
 - On March 27, 2014, the country of India, along with the other 10 countries in the WHO South East Asia Region, was certified polio-free.
 - 80% of the world's people now live in polio-free areas.

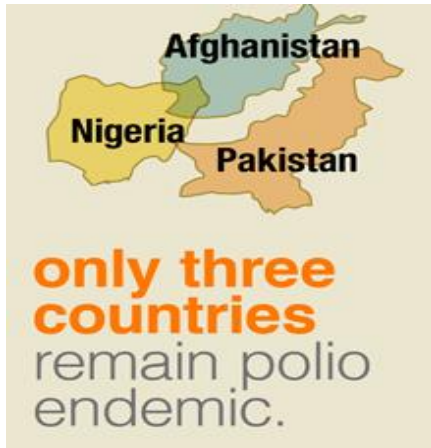
1988



2014*

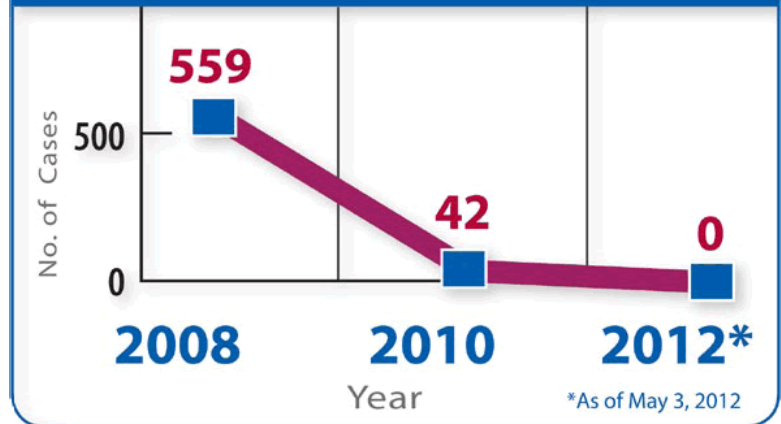


*As of April 29, 2014



<http://www.cdc.gov/polio/progress/>

Poliovirus Cases in India



Polio this week as of 06 May 2020

- The GPEI released a special edition of Polio News which contains the latest on nOPV2 development, the upcoming World Health Assembly in the context of COVID-19, and other updates on the programme. Take a look at the publication.
- A new training to help build knowledge on the standard operating procedures for effective polio outbreak response has been launched. With topics like risk assessment and surveillance, the Polio Outbreak Response training is available for free and the content is aligned with the most recent version of the Polio Outbreak SOPs (v3.1).
- Summary of new viruses this week (AFP cases and environmental samples):
 - Afghanistan: six WPV1 cases, two cVDPV2 cases and four cVDPV2 positive environmental samples
 - Pakistan: two WPV1 cases, 18 WPV1 positive environmental samples and two cVDPV2 cases
 - Malaysia: One cVDPV2 positive environmental sample
 - Chad: One cVDPV2 case and two cVDPV2 positive environmental samples
 - Cote d'Ivoire: Four cVDPV2 positive environmental samples
 - Niger: One cVDPV2 case
 - Nigeria: Three cVDPV2 positive environmental samples

<http://polioeradication.org/polio-today/polio-now/this-week/>

HIV Vaccines?

Why AIDS does not fit the Paradigm for Classic Vaccine Development

- Many vaccines mimic natural immunity
 - No recovered AIDS patients
- Most vaccines prevent disease, not infection
 - HIV infection remains latent for a long time
- Most vaccines protect for many years for organisms that change very little over time
 - HIV mutation rate is very high
- Most vaccines are either live attenuated or whole killed organisms
 - HIV does not retain antigenicity when killed, use of live attenuated virus raises a lot of safety concerns
- Most vaccines prevent against infections that are rarely encountered
 - HIV may be encountered daily by high risk groups
- Most vaccines protect through the mucosal surfaces of the GI and respiratory tracts
 - HIV infection is through the genital tract
- Many vaccines have been tested for safety and efficacy in animal models
 - There is no suitable animal model for HIV/AIDS

Obstacles to the development of HIV vaccine

- Antigenic diversity and hyper-variability of the virus
- Transmission of disease by mucosal route
- Integration of the viral genome into the host cell chromosome
- Transmission of the virus by the infected cell
- Latency of the viral infection
- Sequestration of the virus in the CNS
- Progressive dysfunction and destruction of the immune system of the host
- No spontaneous recovery from natural infection in spite of high level immune responses of the host

HIV Vaccine Strategies

- Preventative Vaccine
- Therapeutic Vaccine
- Immune Responses
 - Antibody responses
 - Cell-mediated responses
 - Both antibody and cell-mediated responses

Ideal HIV Vaccine

- Efficacy in mucosal parenteral route
- Excellent safety profile
- Single dose administration
- Long lived protection after vaccination
- Low cost
- Stable under field conditions (no cold chain)
- Ease of transportation and administration
- Ability to protect against diverse viral isolates

Vaccine Strategies Under Study

Vaccine constituents	Status	Advantages	Disadvantages
Vaccines eliciting anti-HIV antibodies			
Viral surface proteins, such as gp120	In phase I and II trials, which examine safety	Safe and simple to prepare	Vaccine-elicited antibodies have failed to recognize HIV from patients
Whole, killed HIV	Not under study in humans	Should present HIV surface proteins in a relatively natural conformation; simple to prepare	Slight risk that preparations might include some active virus; inactivated virus might shed its proteins and become ineffective
Pseudovirions (artificial viruses containing HIV surface proteins)	Close to phase I trials	Present HIV surface proteins in a relatively natural conformation	Difficult to produce and to ensure long-term stability

Vaccine Strategies Under Study

Vaccine constituents	Status	Advantages	Disadvantages
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Vaccines eliciting cellular responses			
Live vector viruses (non-HIV viruses engineered to carry genes encoding HIV proteins)	In phase II trials	Makers can control amount and kinds of viral proteins produced	Complicated to prepare; current vaccines elicit modest immune response
Naked DNA containing one or more HIV genes	In phase I trials	Simple and inexpensive to prepare	Some worry that integration of HIV genes into human cells could harm patients
HIV peptides (protein fragments)	In phase I trials	Simple to prepare	Do not elicit strong immune response

Vaccine Strategies Under Study

Vaccine constituents	Status	Advantages	Disadvantages
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Vaccines eliciting antibody and cellular responses			
Combinations of elements, such as pure gp120 protein plus canarypox vector	In phase II trials	Should stimulate both arms of the immune response at once	Complicated to prepare
Live, attenuated HIV	Not under study in humans; being assessed in nonhuman primates	Most closely mimics HIV; may interfere with ability of infectious HIV to replicate	Vaccine virus potentially cause AIDS

Types of Experimental HIV Vaccines:

- **Peptide vaccine:** made of tiny pieces of proteins from the HIV virus.
- **Recombinant subunit protein vaccine:** made of bigger pieces of proteins that are on the surface of the HIV virus. Examples of a recombinant subunit protein are gp120, gp140, or gp160 produced by genetic engineering.
- **Live vector vaccine:** non-HIV viruses engineered to carry genes encoding HIV proteins. The genes are inserted into another vector, which carries them into the body's cells. The genes in turn produce proteins that are normally found on the surface of the HIV virus. This type of vaccine most resembles the HIV virus but is not harmful. Many vaccines used today, like the smallpox vaccine, use this approach.
- **DNA vaccine:** uses copies of a small number of HIV genes which are inserted into pieces of DNA called plasmids. The HIV genes will produce proteins very similar to the ones from real HIV.
- **Vaccine combination:** uses any two vaccines, one after another, to create a stronger immune response. Often referred to as "prime-boost strategy."
- **Virus-like particle vaccine (pseudovirion vaccine):** a non-infectious HIV look-alike that has one or more, but not all, HIV proteins.

Novel designs for an HIV-1 vaccine

Design	Limitations
Plasmid DNA	Limited immunogenicity in humans
Live, recombinant vectors:	
Pox viruses	
Vaccinia	Dissemination in immunosuppressed vaccinees
MVA, NYVAC	Limited experience in humans
Canary pox	Limited immunogenicity in humans at achievable dosages
Gene-deleted adenovirus	Pre-existing immunity to adenovirus may limit immunogenicity
alphaviruses, adeno-associated virus	Limited experience in humans
Envelope subunit immunogens	No elicitation of neutralizing antibodies

HIV vaccine candidates in clinical trials

Product	Company	HIV subtype	Phase
Peptide			
C4-V3 peptide	Wyeth	B	1
V3 peptide	CIBG	B	1
p17	Cel-Sci	B	1
Recombinant subunit			
Bivalent rgp 120	VaxGen	B+E	3
Bivalent rgp 120	VaxGen	B	3
Oligomeric gp 140	Aventis	E	1
rgp 120	Chiron	E	1
p24	Chiron	B	1
DNA			
gag	Merck	B	1
env-rev	Wyeth	B	1
Live viral vector			
Vaccinia - env-gag-pol	Therion	B	1
Canarypox - env-gag-pr	Aventis	B	1
Live bacterial vector			
Salmonella -env	Univ Md.	B	1
Combinations (Vector prime + subunit boost)			
Canarypox - env-gag-pr, nef, pol	Aventis	E	2
• rgp 120	Chiron	E	
• rgp 120	Vaxgen	B+E	
Canarypox - env-gag-pr	Aventis	B	2
Salmonella - env	Univ. Med	B	1
(DNA prime+vector boost)			
DNA-gag, pol	Wyeth	B	1
• Canarypox-env, Gag-pr	Aventis	B	1
DNA-env-rev	Wyeth	B	1

HIV vaccine candidates in clinical trials Developing World

Product	Company	HIV subtype	Phase	Site
Peptide				
V3 peptide	CIBG	B	1	Cuba
Recombinant subunit				
Bivalent rpg 120	VaxGen	B+E	3	Thailand
Live viral vector				
Canary pox - env-gag-pr	Aventis	B	1	Uganda
Live bacterial vector				
Salmonella - env	Univ. Md.	B	1	
Combinations (Vector prime + subunit boost)				
Canary pox - env-gag-pr,	Aventis	E	2	Thailand
• Nef, pol rgp 120	Chiron	E		
• rgp 120	VaxGen	B+E		
Canary pox - env gag-pr	Aventis	B	2	Haiti, Trinidad, Brazil

HIV vaccines currently in clinical trials (2002-03)

Vaccine Sponsor	Trial ID	Vaccine type	Description
Phase III			
VaxGen	Vax 004	AIDSVAX B/B	Gp 120 protein vaccine, clade B, being tested in Thailand
Phase II			
NIAID/Aventhis/VaxGen	HVTN 203	ALVAC vCP 1452	Canarypox vaccine (expressing <i>gag</i> , <i>env</i> and <i>pol</i>) with or without AIDSVAX B/B gp 120 boost)
Phase I/II			
NIAID/Aventhis/VaxGen	PACTG 326/ACTG 326	ALVAC vCP 1452	Canarypox vaccine with or without gp 120 boost in babies of HIV positive mothers
Phase I			
ANRS/AVANTIS	VAC 12	LP HIV 1	Lipopeptide (LIPO-4T) express in <i>gag</i> , <i>pol</i> and <i>nef</i> -also includes a CD4 epitope
ANRS/AVANTIS	VAC 10	ALVAC-vCP 1452 +/- lipopeptide	Canarypox and lipopeptides (LIPO-5T, LIPO-6T) separately and in combination
FIT Biotech	NA*	GTU-Nef DNA	HIV-1 <i>nef</i> gene expressed in DNA plasmid vaccine
IAVI/KAVI/DT	IAVI 004	MVA-HIVA	Recombinant vaccinia viral vector, clade A, single dose Kenya
IAVI/MRC	IAVI 005	MVA-HIVA	Recombinant, vaccinia viral boost to volunteers previously vaccinated with DNA prime in IAVI 001
IAVI/MRC/Cobra	IAVI 001	P THr-HIVA	HIV-1 clade A, DNA vaccine, dose response United Kingdom
IAVI/MRC/IDT	IAVI 003	MVA, HIVA	Single dose of recombinant vaccinia viral vector. Clade A- United Kingdom
KAVI/IAVI Cobra	IAVI 002	P THr-HIVA	HIV-1 clade A, DNA vaccine, dose response Kenya
Merck	NA	DNA	Dose response study of <i>gag</i> DNA, clade B
Merck	NA	MRKAd 5	None applying adenovirus vector, clade B, expressing <i>gag</i>
NIAID/Aventis	HVTN 093	ALVAC vCP 1452	Dose response study of canarypox vector, clade B
NIAID/Aventis/VaxGen	AVEG 038	ALVAC vCP 205	Canarypox vaccine boost (expressing <i>gag</i> , <i>pol</i> <i>env</i>) in volunteers who already received pox virus based vaccine
NIAID/Glaxo Smith Kline	AVEG 027	ALVAC vCP 205	Canarypox vaccine with or without VaxGen's gp 120, delivery method also evaluated
NIAID/Glaxo Smith Kline	HVTN 041	Nef-Tat-gp 120 +	Protein vaccine with ASO2A adjuvant (clade B)
WRAIR/Aventis	RV 138	ALVAC vCP 205	Canarypox vaccine delivered either in skin, muscle or dendritic cells in HIV-negative volunteers

Influenza (Flu) Vaccines?

Basic Facts About Flu Vaccine

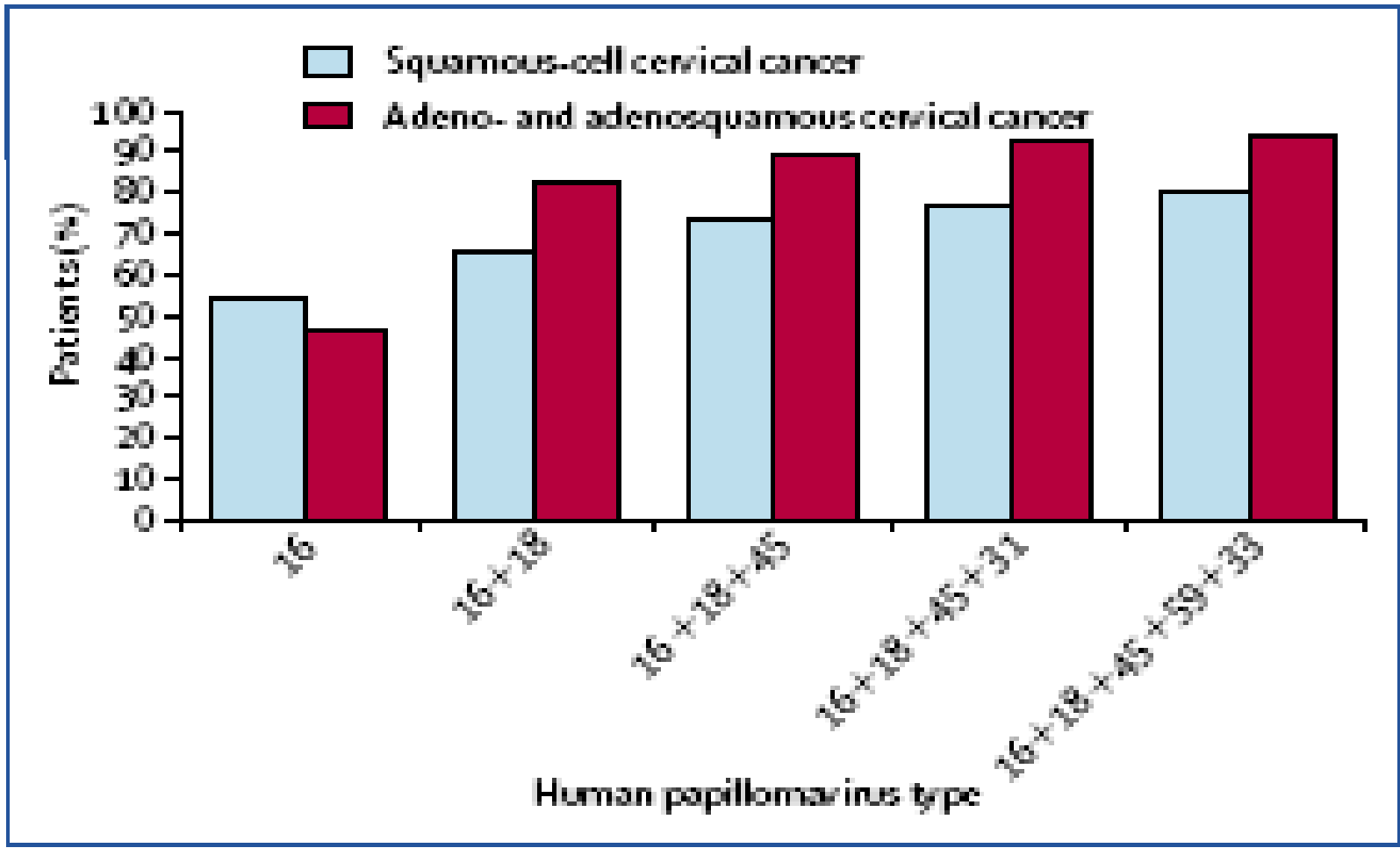
- **The single best way to protect against the flu is to get vaccinated yearly**
- There are two types of vaccines:
 - **The "flu shot"**—an inactivated vaccine, approved for use in people older than 6 months, including healthy people and people with chronic medical conditions.
 - **The nasal-spray flu vaccine** — a live attenuated vaccine (FluMist®) is approved for use in healthy* people 2-49 years of age† who are not pregnant.
- Contains -one A (H3N2) virus, one A (H1N1) virus, and one B virus.
- change each year based on surveillance and estimations
- October or November is the best time to get vaccinated,

How are viruses chosen for the vaccine each year?

- based on previous year strains and how they are changing.
- trends are gathered by 118 national influenza centers in 84 countries
- analyzed by the WHO
- the recommendation is made in February
- FDA makes the final decision in February.
- Manufacturers grow vaccine strains based on these recommendations;

HPV Vaccines

- Cost effective way to prevent disease
- HPV vaccines comprise virus like particles generated by recombinant expression of the major capsid protein, L1, in yeast
 - Forms an empty capsid
 - Immunogenetic
 - Produce high titers of antibodies and cell mediated mediators
 - Immunity is type specific



Cumulative prevalence of HPV types in cervical cancer

Quadrivalent HPV Vaccine

- HPV types 6,11,16,18
- Aluminium-adjutant vaccine
 - Young women negative for HPV
 - Different antibody titers to L1
- Vaccine prevents disease, not infection
- No vaccinee had Cervical intraepithelial neoplasia (CIN)
- In placebo, 7 had CIN and 4 had external genital warts

Table 1: Characteristics of the HPV vaccines Gardasil and Cervarix

Characteristic	Gardasil	Cervarix
Manufacturer	Merck Frosst Canada Ltd.	GlaxoSmithKline Inc.
Type	Prophylactic vaccine consisting of virus-like particles containing L1 capsid proteins	Prophylactic vaccine consisting of virus-like particles containing L1 capsid proteins
Antigens	Quadrivalent vaccine: HPV types 6 (20 µg/dose), 11 (40 µg/dose), 16 (40 µg/dose) and 18 (20 µg/dose)	Bivalent vaccine: HPV types 16 (20 µg/dose) and 18 (20 µg/dose)
Antigen expression system	Yeast	Baculovirus
Adjuvant	Alum: 225 µg aluminum hydroxyphosphate sulfate	ASO4: 500 µg aluminum hydroxide and 50 µg 3-deacylated monophosphoryl lipid A
Dose and schedule	0.5 mL intramuscular injection at 0, 2 and 6 months	0.5 mL intramuscular injection at 0, 1 and 6 months
Availability in Canada	Approved for sale	Not yet available



Harald zur Hausen (born 11 March 1936) is a German virologist and professor emeritus. He has done research on cancer of the cervix, where he discovered the role of papilloma viruses, for which he received the Nobel Prize in Physiology or Medicine 2008.

Table 2: Immune response and disease outcomes* for the HPV vaccines Gardasil and Cervarix

Variable	Gardasil	Cervarix
Published trial results	<ul style="list-style-type: none"> Phase 2 and 3 trials²¹⁻²⁷ 	<ul style="list-style-type: none"> Phase 2 and 3 trials²⁸⁻³¹
Sample size	<ul style="list-style-type: none"> 20 583²⁷ 	<ul style="list-style-type: none"> 18 644³¹
Maximum duration of follow-up	<ul style="list-style-type: none"> 5 years (phase 2)²³ 3 years (phase 3)²⁵ 	<ul style="list-style-type: none"> 5.5 years (phase 2)³⁰ 1.25 (phase 3)³¹
Immune response 1 month after completion of vaccine series	<ul style="list-style-type: none"> Over 99% seroconversion Antibody titres 11 times (HPV type 6), 7 times (HPV type 11), 105 times (HPV type 16) and 19 times (HPV type 18) higher than titres following natural HPV infection²² 	<ul style="list-style-type: none"> Over 99% seroconversion Antibody titres 107 times (HPV type 16) and 82 times (HPV type 18) higher than titres following natural infection²⁸
Duration of immune response	<ul style="list-style-type: none"> 96% seropositive to HPV types 6, 11 and 16 at 24 months 68% seropositive to HPV type 18 at 24 months²⁵ 	<ul style="list-style-type: none"> 100% seropositive to HPV types 16 and 18 at 51-53 months²⁹
Persistent infection† from HPV types 16 and 18	<ul style="list-style-type: none"> Vaccine efficacy 93.5% (95% CI 83%-98%)²³ 	<ul style="list-style-type: none"> Vaccine efficacy 80.4% (95% CI 70%-87%)³¹
Cervical intraepithelial neoplasia (grade 2 or higher) related to HPV types 16 and 18	<ul style="list-style-type: none"> Vaccine efficacy 98% (95% CI 93%-100%)²⁷ 	<ul style="list-style-type: none"> Vaccine efficacy 90.4% (95% CI 53%-99%)³¹
Vaginal and vulvar intraepithelial neoplasia (grade 2 or higher) related to HPV types 16 and 18	<ul style="list-style-type: none"> Vaccine efficacy 97% (95% CI 79%-100%)²⁶ 	<ul style="list-style-type: none"> No data
Persistent infection† of HPV type 45	<ul style="list-style-type: none"> No data 	<ul style="list-style-type: none"> Vaccine efficacy 59.9% (95% CI 3%-85%)³¹
Persistent infection† of HPV type 31	<ul style="list-style-type: none"> No data 	<ul style="list-style-type: none"> Vaccine efficacy 36.1% (95% CI 0.5%-60%)³¹
Protection from genital warts	<ul style="list-style-type: none"> Vaccine efficacy 96% (95% CI 86%-99%)²⁴ 	<ul style="list-style-type: none"> No data

Note: CI = confidence interval.

*All disease outcomes are derived from intention-to-treat analyses for populations that were seronegative and polymerase chain reaction negative at enrolment for all HPV genotypes covered by the vaccine and had received at least 1 dose of the vaccine.

†Persistent infection was defined as 4 months in the Gardasil trial and as 6 months in the Cervarix trial.

Box 2: Knowledge gaps

- Will HPV vaccines affect cervical cancer incidence and mortality?
- Is the priming vaccine series sufficient or will a booster dose be required?
- Will exposure to wild-type HPV contribute to natural boosting?
- Will other HPV genotypes fill the niche previously filled by HPV types 16 and 18?
- How will the vaccination program affect current cytology screening programs?
- Will current cytology screening programs need to be adapted to identify vaccine failures?
- Are there rare but serious adverse effects of vaccination that have not yet been detected?

Therapeutic Vaccines

- For high risk HPV types are undergoing clinical trials
 - Immune response: cell mediated factors
 - Focus: HPV E6 and E7 proteins
 - Ubiquitously expressed in cervical cancers
- BCG + HPV E7 caused tumor regression in mice

Prevention

- Primary: Education about HPV to Vaccines
 - Safe sex practices
- Secondary: Pap smear screening

HPV Vaccine

- The quadrivalent vaccine, Gardasil®, protects against four HPV types (6,11,16, 18), which are responsible for 70% of cervical cancers and 90% of genital warts
- Licensed by FDA on June 8, 2006
- ACIP voted to recommend use of this vaccine in females, ages 9-26 years
- The vaccine is made from non-infectious HPV-like particles (VLP)

HPV Vaccine

- HPV infections are largely shielded from the host immune response because they are restricted to the epithelium
- The best characterized and most type-specific antibodies are those directed against conformational epitopes of the L1 capsid protein assembled as VLPs

HPV Vaccine

- The L1 major capsid protein of HPV is the antigen used for HPV vaccination (105).
- Using recombinant DNA technology, the L1 protein is expressed in *Saccharomyces cerevisiae* (yeast), and the proteins self-assemble into conformationally intact, noninfectious VLPs. Each 0.5-mL dose contains 20 μg HPV 6 L1 protein, 40 μg HPV 11 L1 protein, 40 μg HPV 16 L1 protein, and 20 μg HPV 18 L1 protein. VLPs are adsorbed on an aluminum-containing adjuvant.
-
- Each 0.5-mL dose contains 225 μg amorphous aluminum hydroxyphosphate sulfate. The formulation also includes sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection.
- The quadrivalent HPV vaccine contains no thimerosal or antibiotics.

HPV Vaccine

- The vaccine has a 100% efficacy in preventing cervical precancers caused by the targeted HPV types, and nearly 100% efficacy in preventing vulvar and vaginal precancers and genital warts caused by the targeted HPV types
- However, the vaccine has no therapeutic effect on HPV-related disease

HPV Vaccine

- The vaccine should be delivered through a series of three intra-muscular injections over a six-month period. The second and third doses should be given 2 and 6 months after the first dose
- The private sector list price of the vaccine is \$119.75 per dose (about \$360 for full series)

HPV Vaccine

- A bivalent HPV vaccine is in the final stages of clinical testing in females.
- This vaccine would protect against the two types of HPV (16,18) that cause 70% of cervical cancers

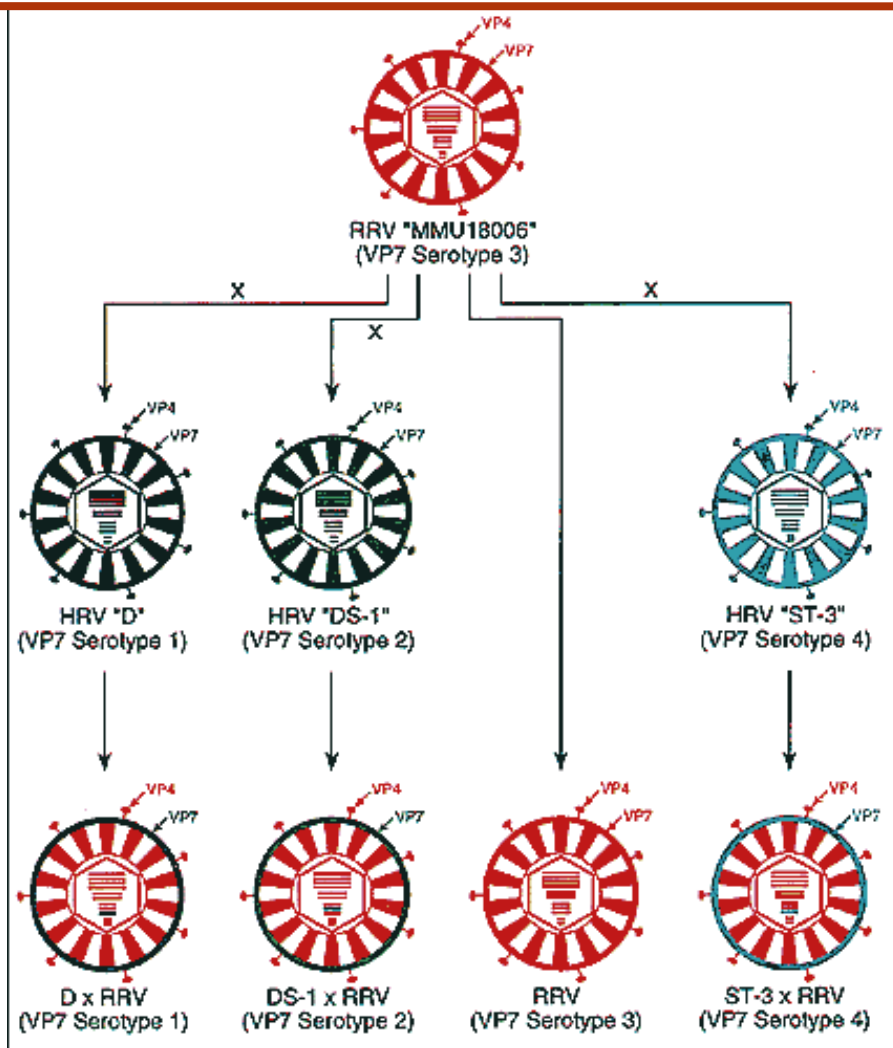
Rotavirus vaccine

- Monovalent Vaccines
 - Live attenuated vaccine derived from nonhuman host rotaviruses such as bovine and rhesus
- Reassortant Vaccines
 - animal-human reassortants expressing VP7 proteins used as immunogens such as rhesus-human reassortant or bovine-human reassortant vaccines



(Picture Source: www.ismp.org/Images/rotavirus.g)

Rotavirus vaccine (cont.)



- Production of reassortant tetravalent vaccine with VP7 serotype 1-4 specificity
- co-infection of RRV with HRV serotype 1,2, and 3
- safe and immunogenic

(Picture Source: <http://www.cdc.gov/ncidod/EID/vol4no4/parasharG>)

Prevention of Hepatitis B

- Safe sex practices
- Avoidance of needlestick injuries or injection drug use
- Active and passive prophylaxis

Prevention of exposure to hepatitis B virus

Preventing direct exposure

Avoidance of mucosal contact or parenteral intrusion with/by

Infected body fluids and secretions

Infected blood or blood products

Needle sharing, intravenous drug use

Unprotected sex

Infected patient–doctor contact

Contact via abrasions and open lesions

Preventing indirect exposure

Renal dialysis

Fomites

Medical instruments, acupuncture, needle stick

Environmental exposure—wounds and scratches

Passive prophylaxis

- ISG

- Anti-HBs (HBIG)

- Prepared from persons with high titers of HBsAg but are free of the antigen itself.
 - Reduces disease if administered immediately after exposure
 - Postexposure passive prophylaxis must be followed by active immunization with vaccine

Active Prophylaxis (Immunization)

- Inactivated Hepatitis B vaccine
 - Have been available for several years
 - First developed by purification and inactivation of HBsAg from blood of chronic carriers
 - No longer in use

- Recombinant HBsAg grown in yeast
 - Current vaccine
 - Excellent protection has been shown in MSM/Medical personnel
 - High risk groups should be vaccinated
 - Laboratory workers, Injection drug users, Children (Recently)

Prevention of vertical transmission

- Combination active and passive prophylaxis
 - Most effective approach to prevent neonatal acquisition and development of chronic carrier state in neonate

- Routine screening of pregnant women for HBsAg
 - Infants born to HBsAg⁺ women are given HBIG immediately followed by three doses of Hepatitis B vaccine within 24hrs of birth

 - Similar combination is used for unimmunized persons exposed by needlestick or similar injuries.
 - Procedure varies depending on the Hepatitis B status of the 'donor' linked to the injury



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Vaccine 21 (2003) 4626–4649

Review

Critical overview and outlook: pathogenesis, prevention, and treatment of hepatitis and hepatocarcinoma caused by hepatitis B virus

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Review

Overview of the pathogenesis, prophylaxis and therapeutics of viral hepatitis B, with focus on reduction to practical applications[☆]

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- Plasma derived vaccine (Blumberg, 1981)
- Recombinant yeast-derived vaccine (1986)
 - Vaccine performance
 - Strategies for vaccine utilization
 - Economic analysis of benefit from vaccination
 - Legacy and future of Hepatitis B vaccines

Research and development of hepatitis B vaccines

Hepatitis B virus does not grow in cell culture

- 1965 Blumberg discovery of surface antigen opens door to vaccine
 - 1968 Pioneering studies initiated in our laboratories to purify antigen and to inactivate all life forms
 - 1971 Process developed, safety established in vitro, antigen formulated in alum, potency shown for plasma-derived vaccine
 - 1973 Safety and efficacy established in chimpanzee studies
 - 1975 Clinical safety shown
 - 1980 High-level protective efficacy shown in clinical trials
 - 1981 Plasma-derived vaccine licensed
 - 1975 Collaborative venture started to attempt recombinant expression in yeast. Success achieved
 - 1980 Process developed for purification of antigen from yeast
 - 1982 Yeast-derived antigen substituted for plasma-derived antigen in vaccine
 - 1986 Yeast-derived vaccine licensed
-

Performance of hepatitis B vaccine

Paradigm for a safe and effective vaccine

In adults, protection in near 100% of antibody responders.

Overall efficacy 95%

In newborn infants born to *e* antigen positive mothers — vaccine overcomes tolerance and immunizes in at least 75%

In babies from non-carrier mothers, protection is near 100%

Lasting immunity, with strong anamnestic memory

Economic analysis for vaccination benefits

Great societal benefits may derive from vaccination, but policy for vaccine use is based on cost effectiveness

Cost effectiveness is based on the savings in medical treatment and time lost per dollar spent for vaccination. Thus, the cost per unit of benefit

The World Bank measures benefit in terms of cost for each disability adjusted life year saved. Thus, DALY

Six vaccines used by the Expanded Program on Immunization cost less than \$25.00/DALY

The cost for universal infant immunization against hepatitis is estimated at \$25–50 per DALY using purchased vaccine

General view by World Bank:

A cost of less than \$100 per DALY is a good buy

Utilization of hepatitis B vaccine

Universal immunization of all newborn — at least 90 nations

Immunization of all high-risk persons and adolescents — some nations

Worldwide immunization — will gradually reduce the 350 million carrier pool and the deaths from liver disease

Worldwide focus on newborn alone — will require at least one generation to bring hepatitis under substantive control

Nationwide immunization program in Taiwan — reduced liver cancer in 12–14-year-old children by 75%

The legacy and future of hepatitis B vaccine

Hepatitis B is a disease for which a solution already exists

The solution lies with global immunization of all susceptibles

Elimination/eradication of the infection could bring huge cost savings

High cost of disease and disability eliminated

High cost for research could be diverted to medical problems that still need to be solved

United Nations General Assembly — declaration that protection by vaccines is a basic human right

Global Alliance for Vaccine Initiatives (GAVI): current major force to develop and bring vaccines to all peoples

Gates Foundation brings economic reality to vaccine initiatives

Real value is given when medical science brings health to all nations for the betterment of mankind

Editorial

Global Control of Primary Hepatocellular Carcinoma with Hepatitis B Vaccine: The Contributions of Research in Taiwan

Mark A. Kohn¹

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- Contribution of research in Taiwan
 - One of the most important epidemiological studies in the 20th century
 - Beasley *et al*, 1981
 - 22,000 male Taiwanese healthcare workers for more than a decade with almost complete follow up
 - Rates of Primary Hepatocellular Carcinoma (PHC) were 100 times higher among men who were HBsAg⁺ (495/100,000 per year)
 - Rates of PHC were 5/100,000 per year in those who were HBsAg⁻

Eradication of viral diseases

- Elimination vs eradication
 - Elimination: interruption of transmission within a region
 - Eradication: elimination from the world

- So far only smallpox has been eradicated globally
 - In 1977 last case was reported in Somalia
 - Vaccination and surveillance/containment programs were successful

- Next targets:
 - Measles and polio
 - No animal reservoir, no recurrent infection, few serotypes, effective vaccines

Discuss biological and socio-political/economical features of measles and polio that are similar/different from smallpox and that has affected the global eradication efforts!!!

Current Bacterial Vaccines

Bacteria (Disease)	Vaccine Components	Target Population
<i>Bacillus anthracis</i> (anthrax)	Killed cell	Sheep fur handlers; military; biodefense
<i>Yersinia pestis</i> (plague)	Killed cell	Animal handlers, veterinarians, biodefense
<i>Francisella tularensis</i> (tularemia)	Live attenuated	Animal handlers, biodefense
<i>Coxiella burnetti</i> (Q fever)	Inactivated	Sheep handlers, lab personnel
<i>Mycobacterium tuberculosis</i> (TB)	Live attenuated BCG	Endemic areas
<i>Borrelia burgdorferi</i> (Lyme disease)	Subunit	Endemic areas

Immune Globulins Available for Post-exposure Prophylaxis

Disease	Source
Hepatitis A	Human
Hepatitis B	Human
Measles	Human
Rabies	Human
Chickenpox, zoster	Human
Cytomegalovirus	Human
Tetanus	Human, equine
Botulism	Equine
Diphtheria	Equine
Smallpox	Human (limited supply)

Major diseases for which vaccines are not available or suboptimal

Disease	Estimated annual mortality	Estimated annual incidence
Malaria	1,124,000	300-500 million
Schistosomiasis	15,000	Numbers unavailable
Worm infestation	12,000	Numbers unavailable
Tuberculosis	1,644,000	~8 million
Diarrheal disease	2,001,000	~4,100 million
Respiratory disease	3,947,000	~362 million
HIV/AIDS	2,866,000	~2 million
Measles*	745,000	~44 million

*Current vaccine heat-sensitive → use difficult in tropical countries.

Data based on WHO estimates, 2001.

New approaches to vaccine development

- Application of molecular biology, genomics & bioinformatics to develop new vaccines
 - Hybrid virus vaccines
 - Attenuated viral vectors (vaccinia, canarypox)
 - Often replication defective
 - Genetically engineered live bacterial vaccines
 - Genetically engineered subunit vaccine
 - Variety of prokaryotic and eukaryotic expression systems (including plants) for production of pathogen antigen
 - Peptide subunit vaccines
 - Dendritic cell vaccines for cancer immunotherapy
 - DNA vaccines
 - Identification of novel vaccine antigens by genomic/bioinformatic approaches

COVID-19 vaccine development pipeline gears up



Vaccine makers are racing to develop COVID-19 vaccines, and have advanced ten candidates into clinical trials. But challenges remain. Asher Mullard reports.

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	Developer	Properties	Development status
mRNA-1273	Moderna and NIAID	mRNA vaccine	Phase 2
BNT162	BioNTech and Pfizer	mRNA vaccine	Phase 1/2
INO-4800	Inovio Pharmaceuticals	DNA vaccine	Phase 1
AZD1222	University of Oxford and AstraZeneca	Adenovirus vaccine	Phase 2b/3
Ad5-nCoV	CanSino Biologics	Adenovirus vaccine	Phase 2
Unnamed	Wuhan Institute of Biological Products and Sinopharm	Inactivated virus	Phase 1/2
Unnamed	Beijing Institute of Biological Products and Sinopharm	Inactivated virus	Phase 1/2
PiCoVacc	Sinovac	Inactivated virus, plus adjuvant	Phase 1/2
Unnamed	Institute of Medical Biology and Chinese Academy of Medical Sciences	Inactivated virus	Phase 1
NVX-CoV2373	Novavax	Protein subunit	Phase 1/2

Table: COVID-19 vaccines in clinical trials

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