Antiviral therapy and vaccination

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Contents

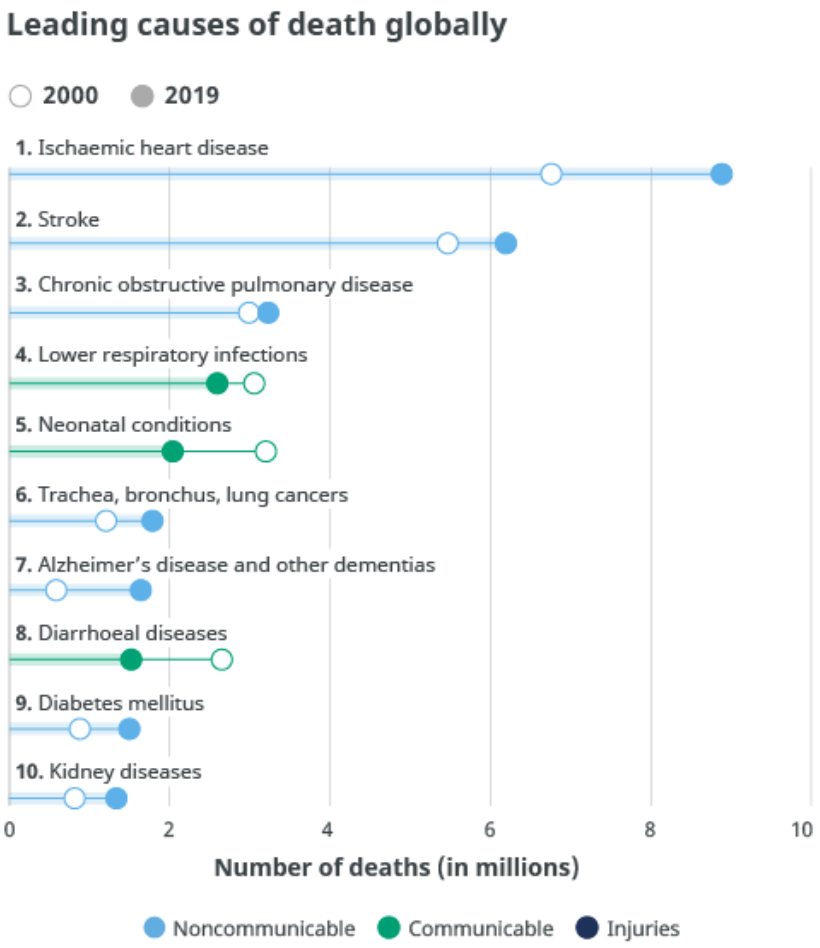
Vaccines

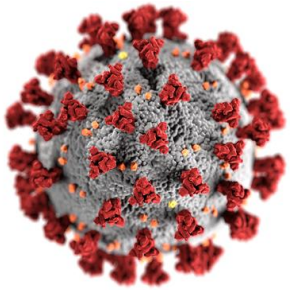
- Active and passive vaccines
- Different types of active vaccines
- Vaccine developement

Antivirals

- Mechanisms of Action
- Drug Resistance
- Antiviral developement

Global burden of infections





Illness	Infections	Mortality (year)
Influenza	~5 Mio	~650.000
HIV	39 Mio	~630.000
Diarrhoeal disease (Rota, Adeno….)	1.7 Billion	1.6 Mio
Hepatitis B	296 Mio	820.000
Hepatitis C	58 Mio	290.000

World Health Organization (WHO)

Antiviral strategies

Hygiene etc.

Vaccines

Antiviral drugs

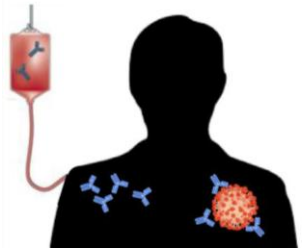
Active – Passive vaccination

Active - modified form of the pathogen or material derived from it that induces immunity to disease

- ***Long term protection after latency*** *(duration variable)*

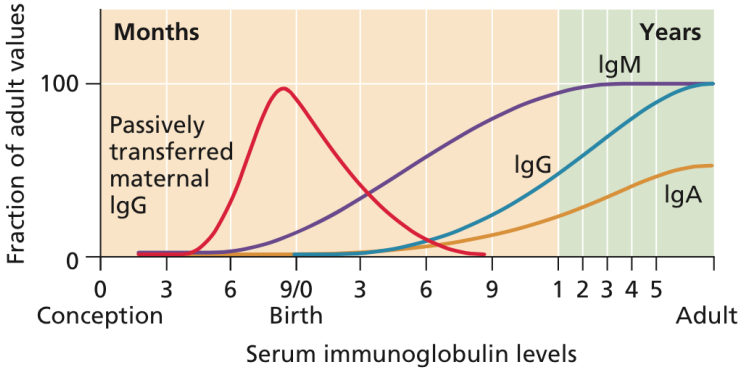
Passive - products of the immune response (antibodies or immune cells) into the recipient

- ***Short term protection*** *(several weeks to 2-3 months)*

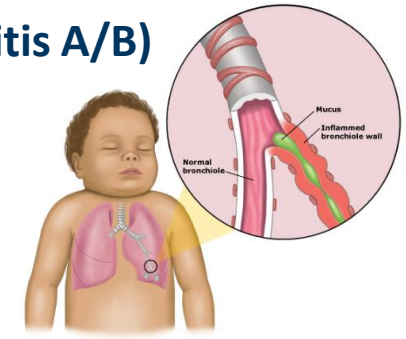


Passive vaccination

Maternal passive immunity



Emergency/preventive measure: (Rabies, tetanus, RSV, Hepatitis A/B)



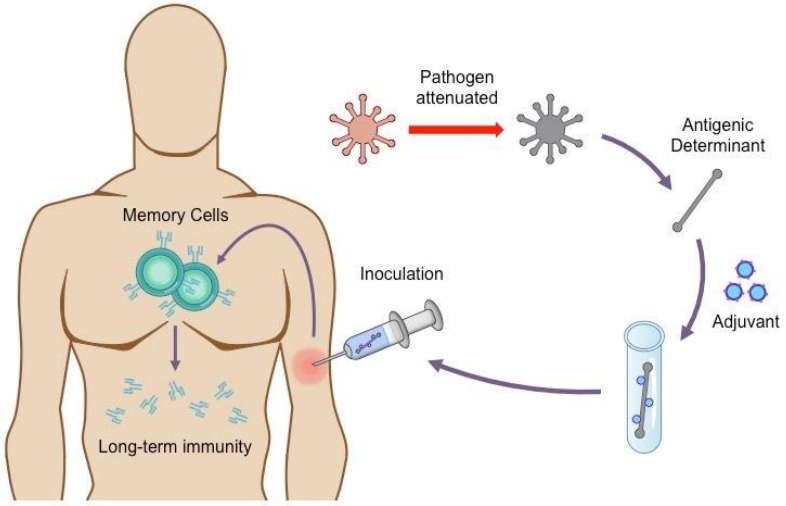
RSV: Prophylaxis with palivizumab in high-risk groups

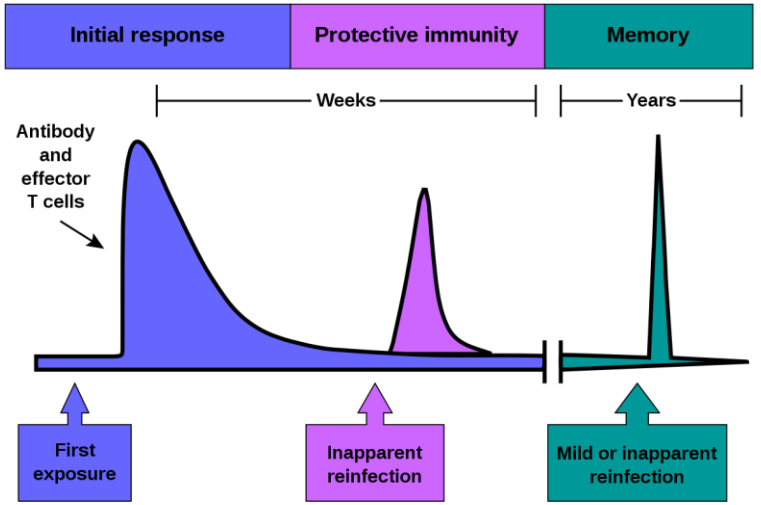
Rabies:

- Virus infects central nervous system
- Transmission by infected animals (saliva)
- Almost always fatal
- Post-exposure vaccination within 24 hours

COVID19: prophylaxis patients at risk for severe covid 19 symptoms.

Active vaccination





Pathogen derrived antigens to mobilize host immune system to protect against viral infection or disease (protective immunity).

Establishment of an immune memory (long lived B/T memory cells)

Layers of protection

Individual protection:

Individuals can no longer become (severely) ill

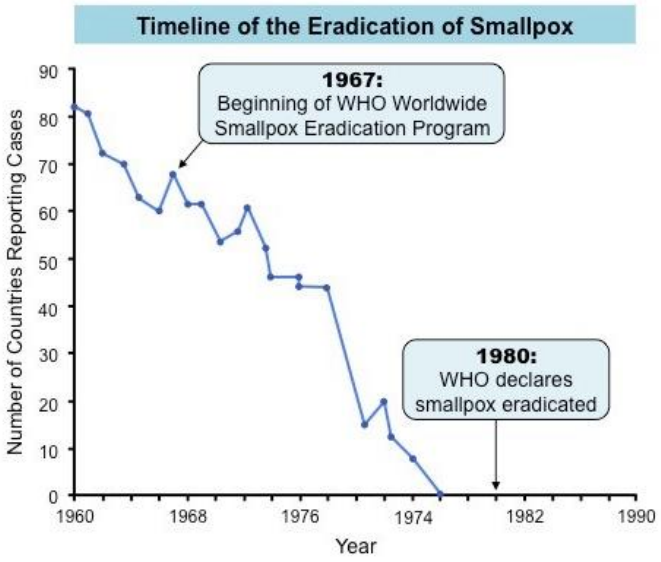
Prevention only possible by individual protection (e.g. FSME; tetanus)

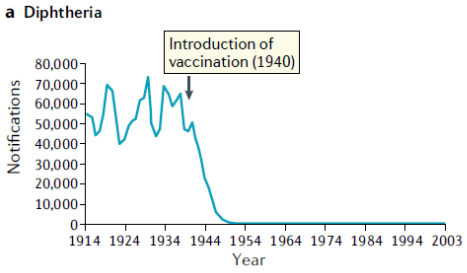
Smallpox

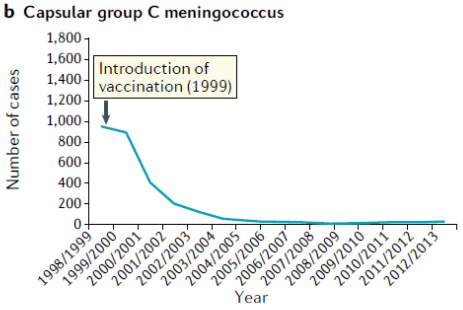
Edward Jenner 1796

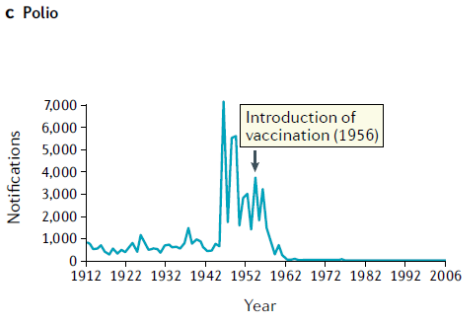
- Variola virus (DNA virus)
- Mortality rate: >30%, >80% in infants
- 300 million deaths during 20th century (eradicated 1980)
- Monkeypox Vaccine

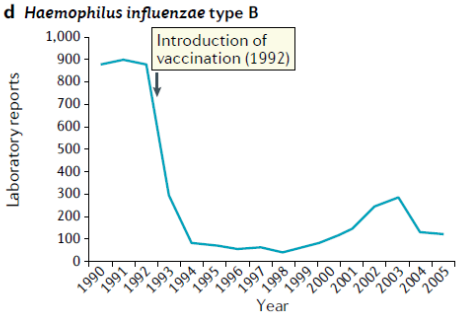
Vaccination campaigns

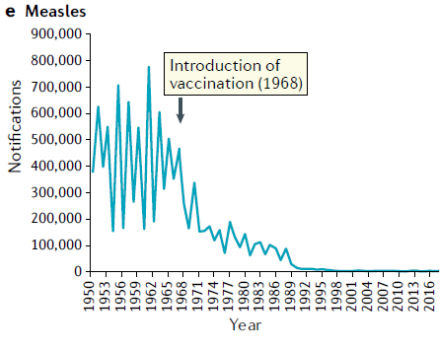


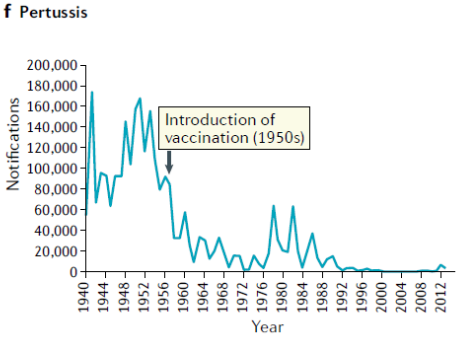




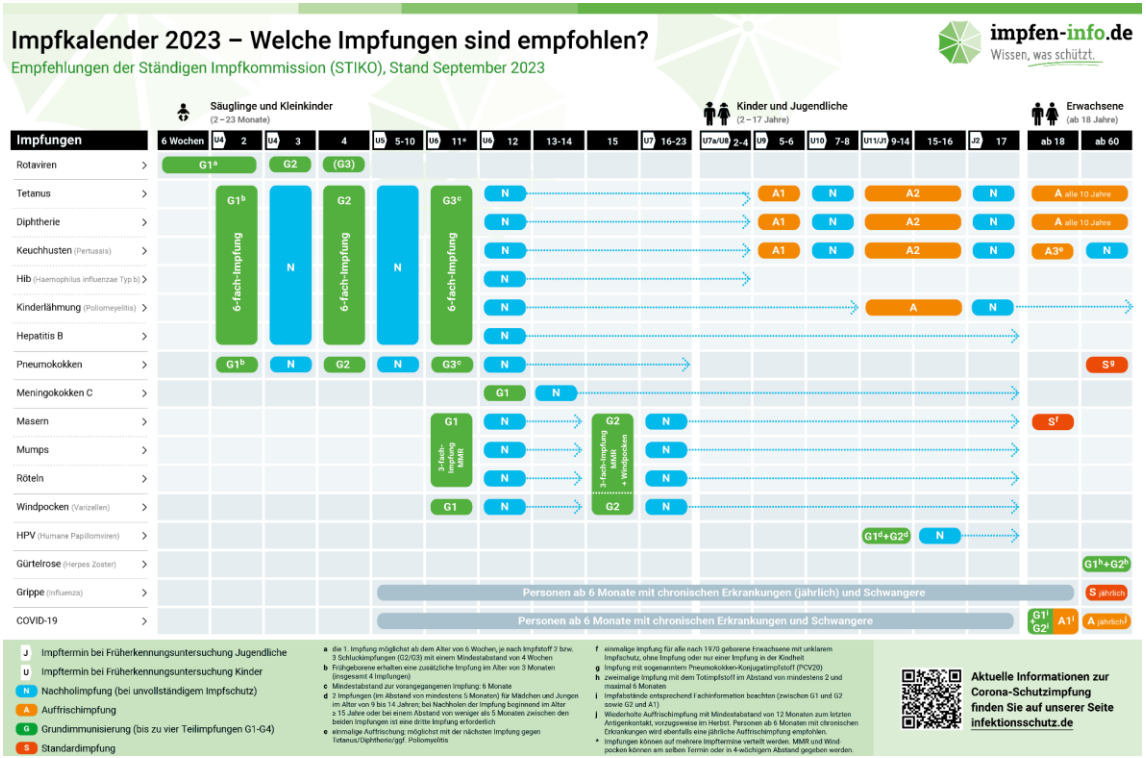








Immunization schedule (STIKO)



Vaccines without „universal“ indication:

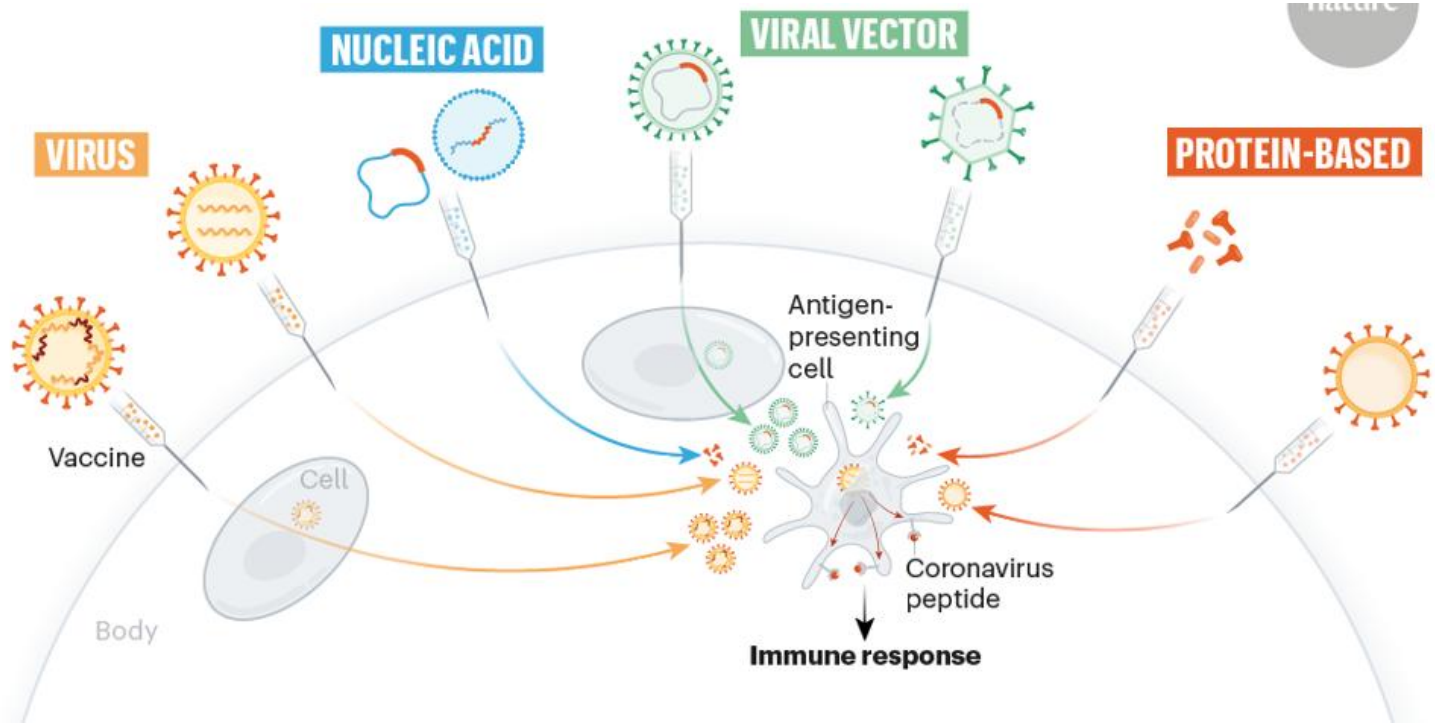
- Hepatitis A
- Japanese Encephalitis
- Rabies
- Smallpox
- Yellow Fever

Source: STIKO, Robert Koch Institut (www.rki.de)

- Memory depends on vaccine recipient (age etc.), antigen, booster etc.

→ Vaccine-dependent administration schedules

Types of vaccines



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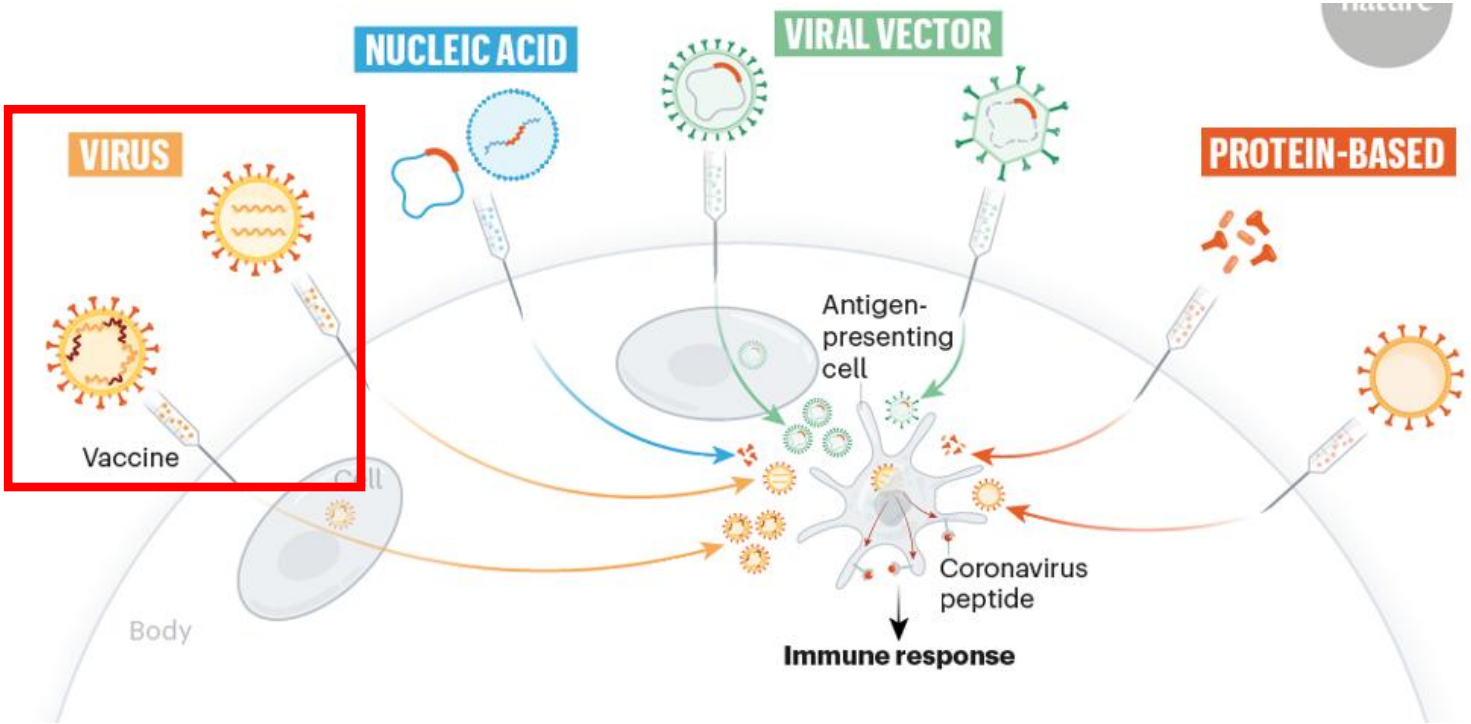
Types of vaccines



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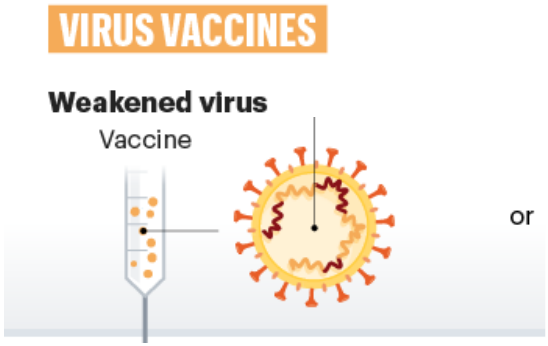
Virus vaccines



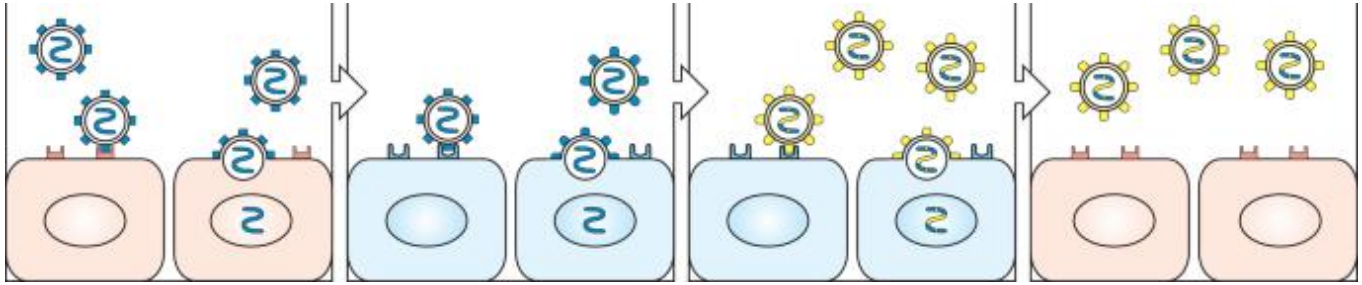
Attenuated virus

- Attenuated viable pathogens
- "Physiological" stimulation of the immune system (long lasting protection)
- Limited use in certain patient groups (immunosuppressed patients)

Live vaccines

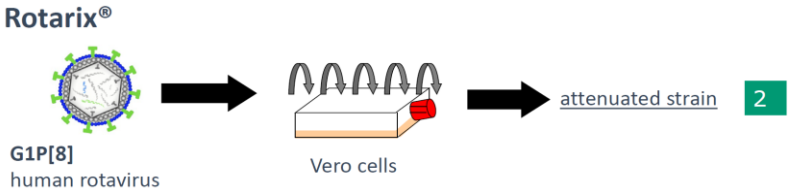
Mumps, measles, rubella and chickenpox:

- 3(4)-dose combination vaccine (MMR(V)).
- Attenuated viruses from human cells or embryonic chicken cells
- Contraindications: Immunodeficiency/pregnancy/chicken protein allergy.

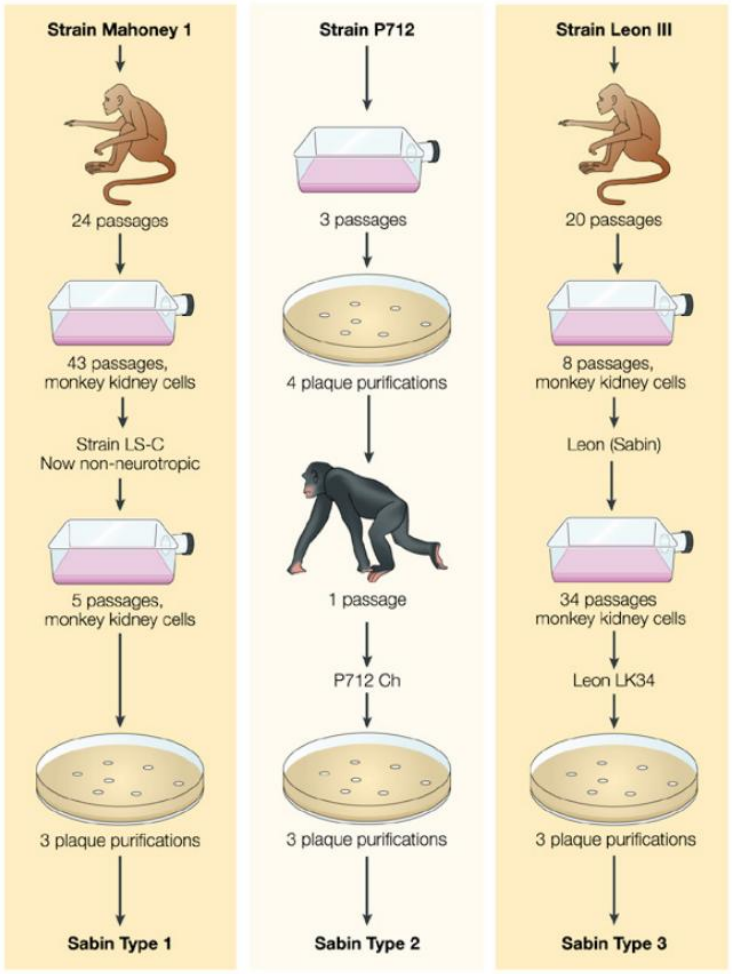


Rotavirus

- Attenuated virus from Vero cells
- STIKO recommendation for infants
- Oral vaccination

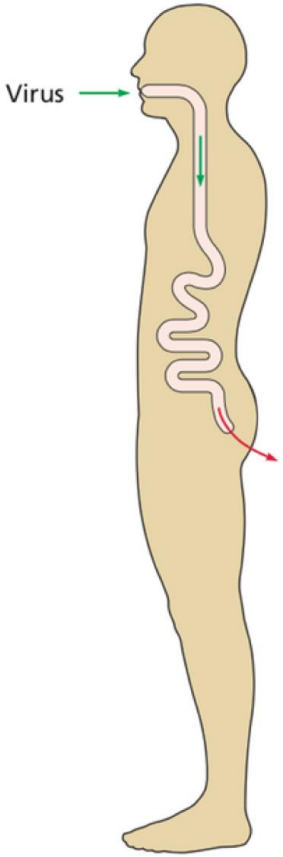


Poliovirus



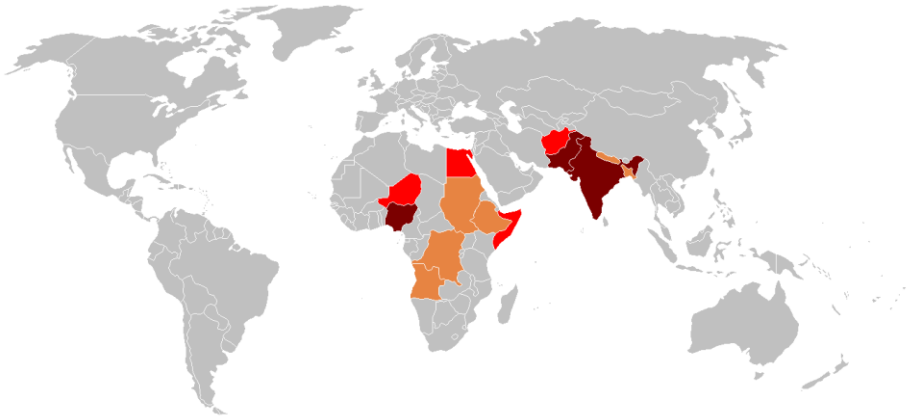
Virus	Mutation
P1/Sabin	5'-UTR nt 480 VP1 aa 1106 VP1 aa 1134 VP3 aa 3225 VP4 aa 4065
P2/Sabin	5'-UTR nt 481 VP1 aa 1143
P3/Sabin	5'-UTR nt 472 VP3 aa 3091

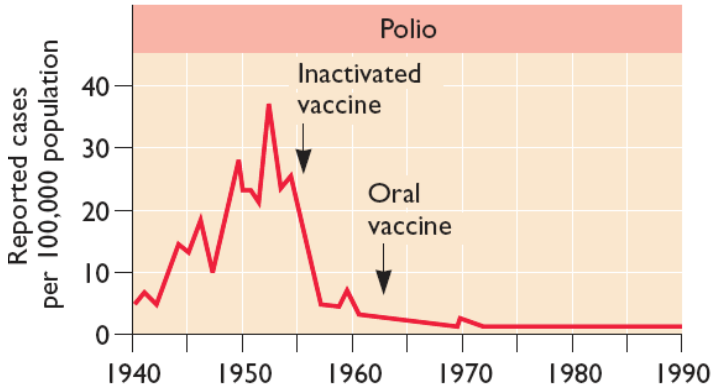
Oral poliovirus vaccine



Vaccine-induced polio if vaccine strains revert (1 in 2.7 million)

Poliovirus





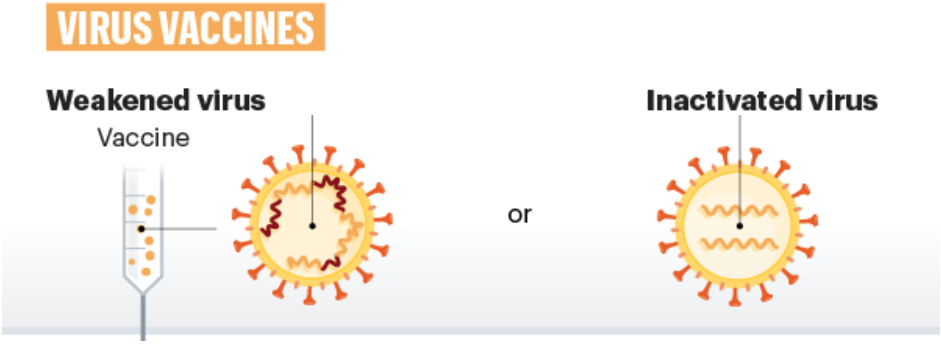
Oral polio vaccines (Sabin)

- Attenuated poliovirus types 1, (2) and 3
- Better immune response
- Lower cost, easier to use

Inactivated poliovirus vaccine (Salk)

- Injection, routinely used
- Inactivation with formaldehyde
- Not STIKO recommended

Virus vaccines



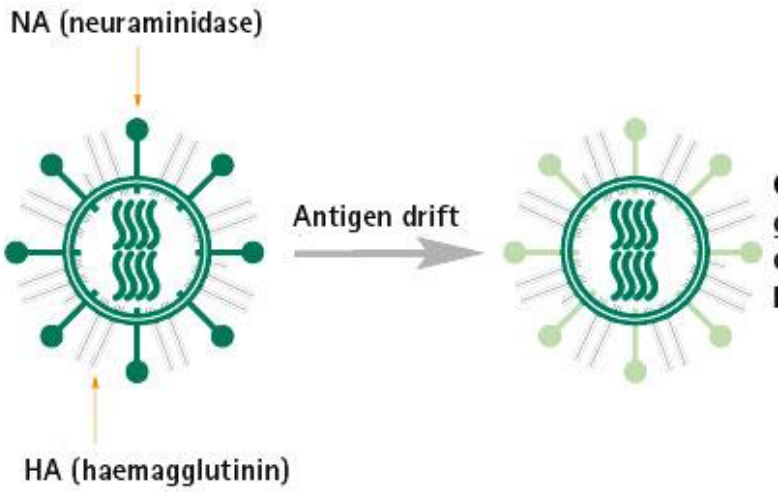
Attenuated virus

- Attenuated viable pathogens
- "Physiological" stimulation of the immune system (long lasting protection)
- Limited use in certain patient groups (immunosuppressed patients)

Inactivated virus

- Chemical inactivation → No danger of infection
- Basic immunization with 2-3 injections
- Boosters
- Often with adjuvants

Influenza



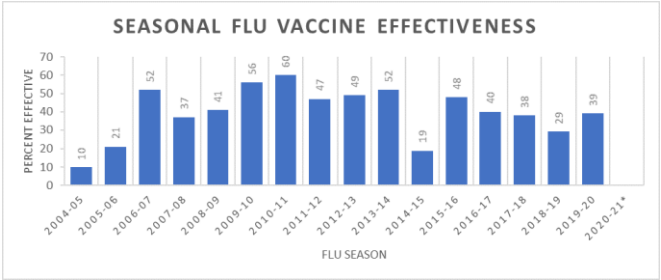
World Health Organization

Recommended composition of influenza virus vaccines for use in the 2019-2020 northern hemisphere influenza season

21 February 2019 ***(updated on 21 March 2019)***

It is recommended that egg based quadrivalent vaccines for use in the 2019-2020 northern hemisphere influenza season contain the following:

- an A/Brisbane/02/2018 (H1N1)pdm09-like virus;
- an A/Kansas/14/2017 (H3N2)-like virus; *
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage); and
- a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage).

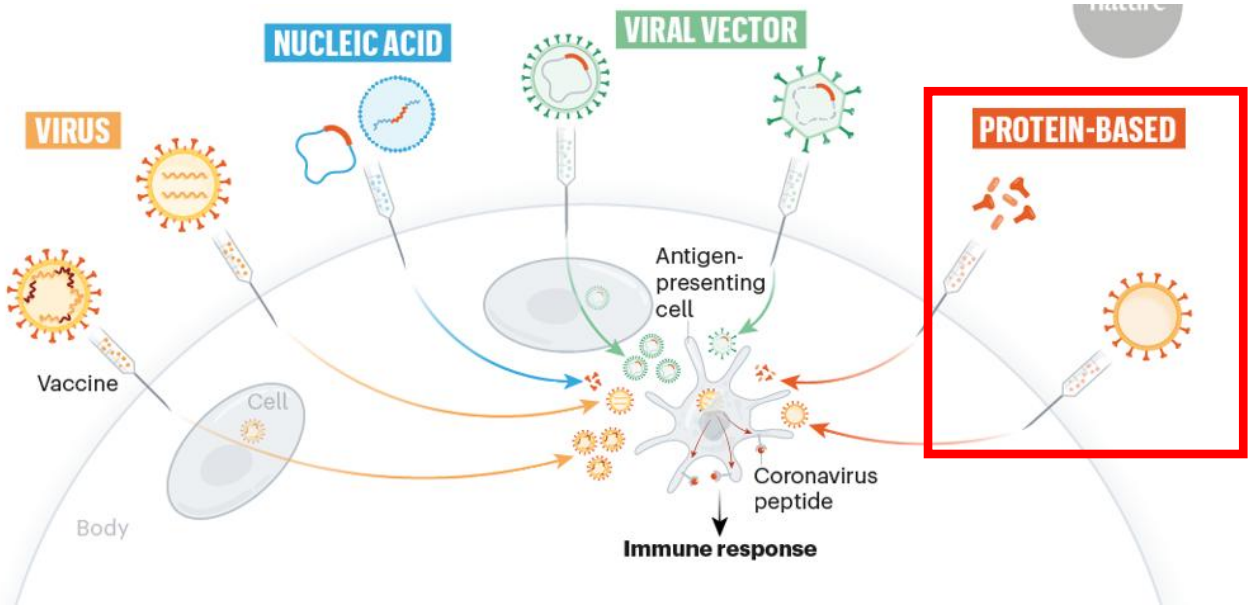


estimates from the U.S. Flu VE Network

- Inactivated virus
- Envelope proteins continuously change (Antigen Drift)

→ Annual adaptation to circulating virus types (variable protection)

Vaccine types



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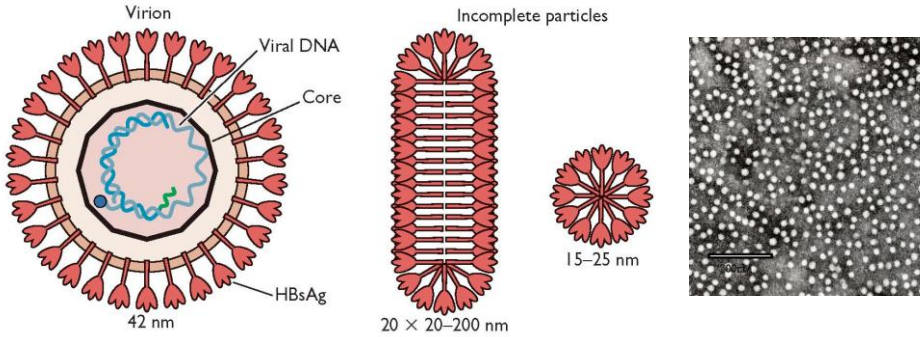
Subunit vaccines

- Recombinant or purified protein vaccines (No virus cultivation)
- No live components → no risk of the vaccine triggering disease

Virus-like-particles

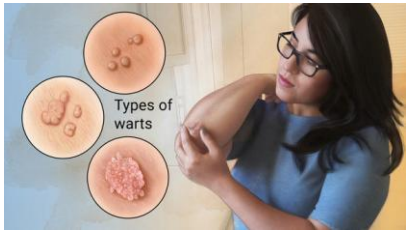
Hepatitis B Virus

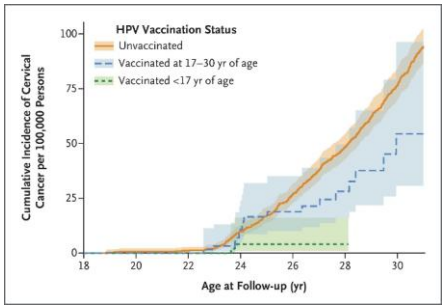


HBsAg produced in yeast → Assembly into empty particles (VLP)

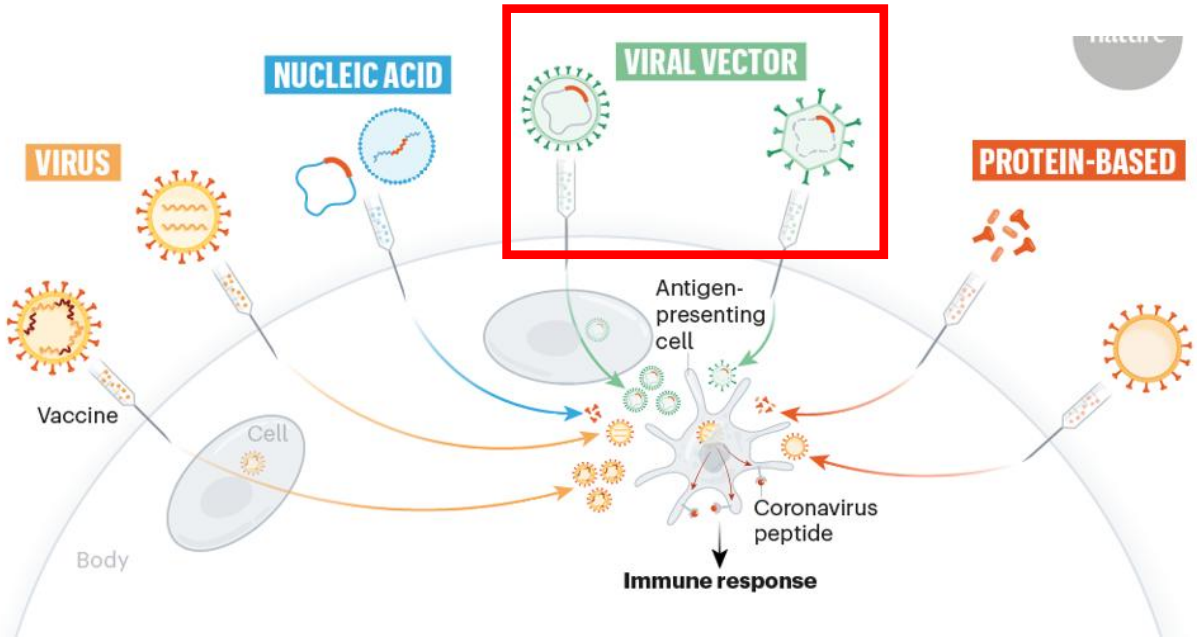
Human papillomaviruses (HPV)

- Capsid of four papillomavirus types
  → empty HPV viral envelopes
- Cancer prevention (cervical cancer)





Vaccine types



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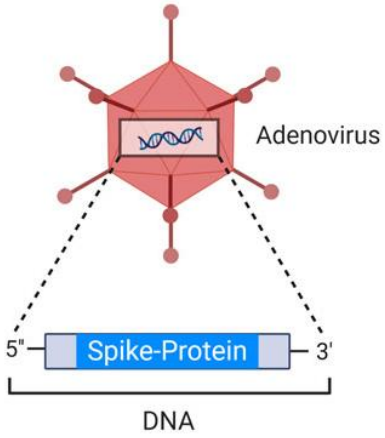
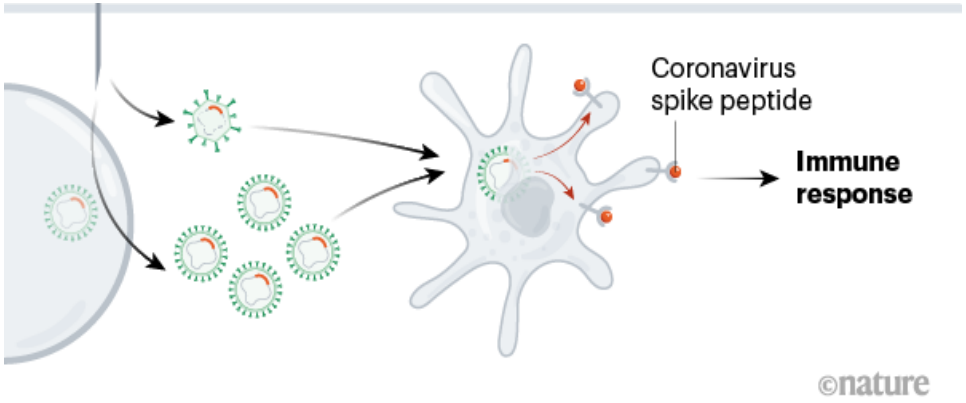
Vector vaccines:

- Recombinant carrier virus encoding for antigen(s) of the target pathogen
- Replicating and non-replicating

SARS-CoV2 vector vaccines



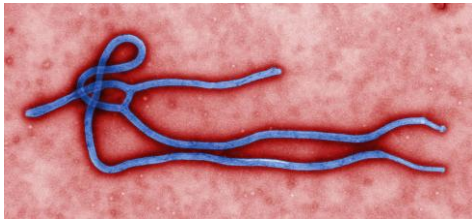


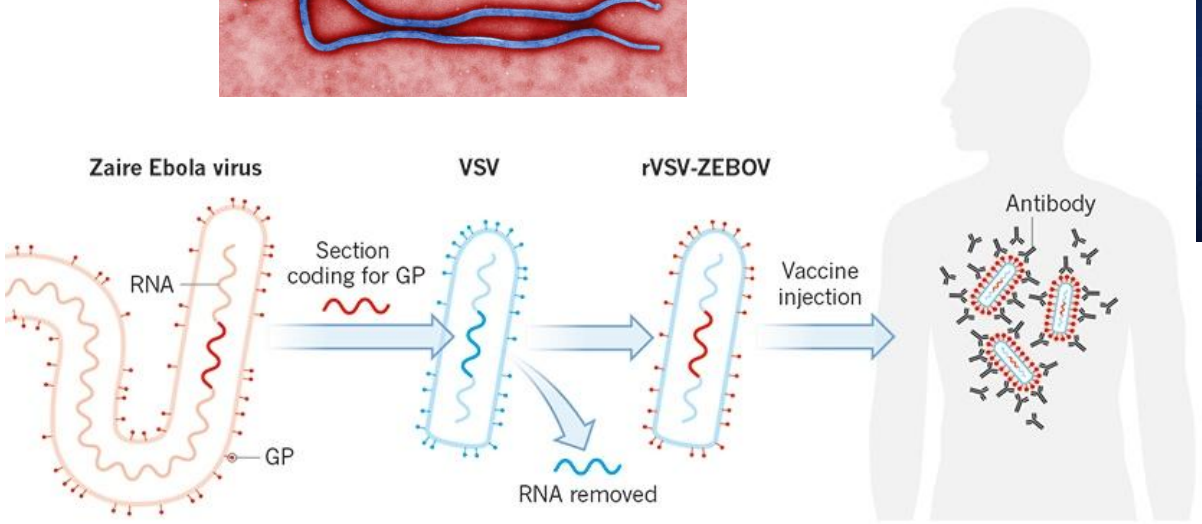
- Ad26.COV2.S (Johnson&Johnson)
- Vaxzevria (Astra Zeneca)
- Sputnik V (Russia)

- Adenoviruses with SARS-CoV2 spike (not replication-competent)

- Strong immune response (cellular + humoral).

Ebola vector vaccine

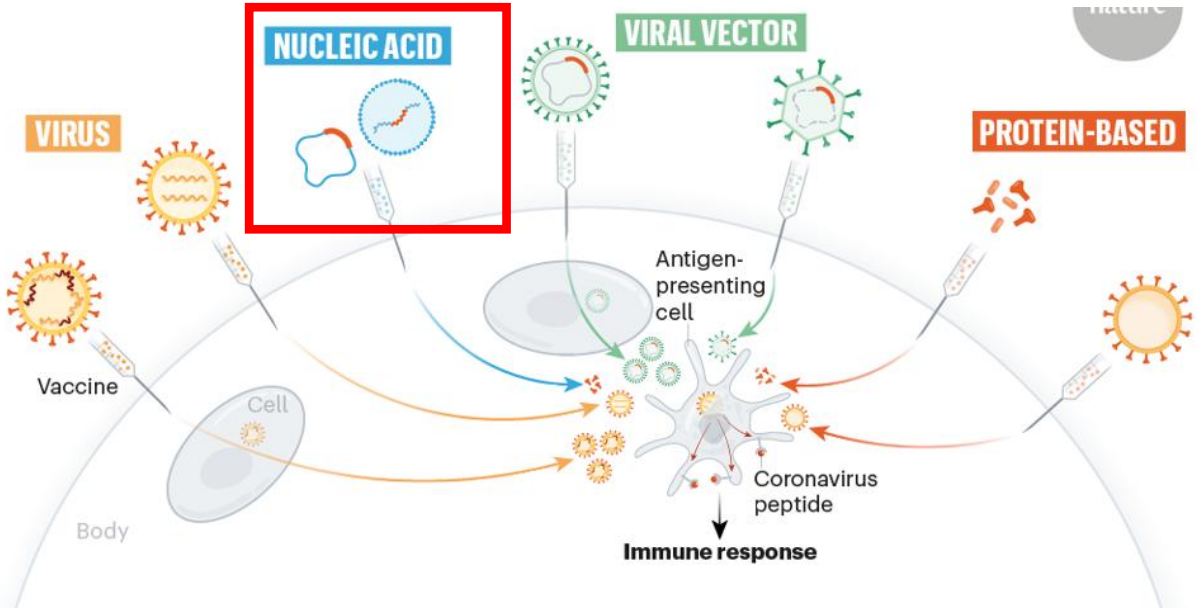




rVSV-ZEBOV

- Pseudotyped VSV (common laboratory virus)
- Recombinant, replication-competent vaccine
- Approved in 2019 (highly effective (70-100%))

Vaccine types



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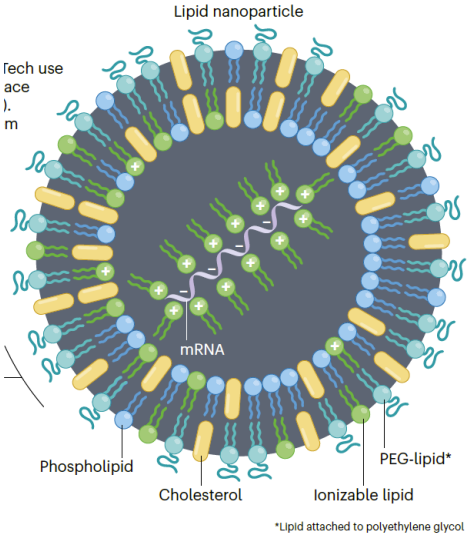
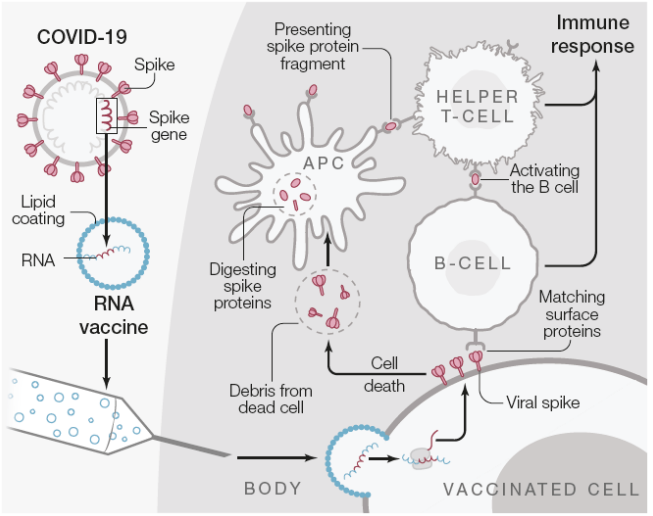
Gene-based vaccines:

- Genetic information for target antigens of the pathogens (DNA/mRNA)

mRNA Vaccines - SARS-CoV-2

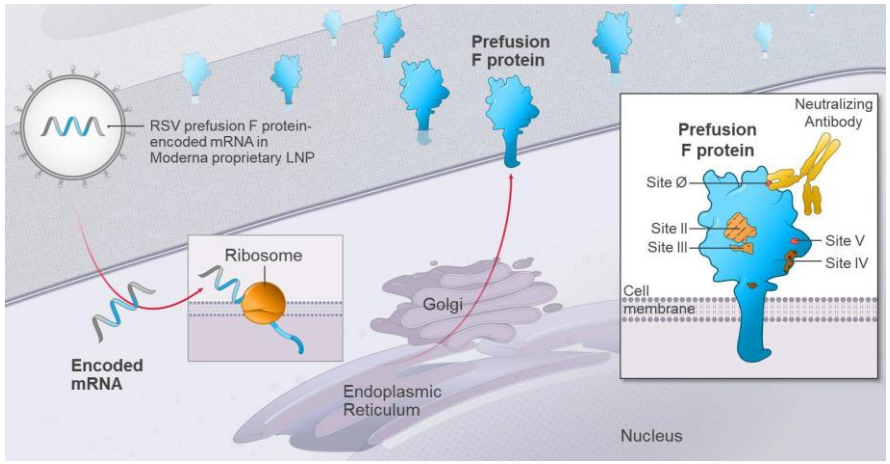


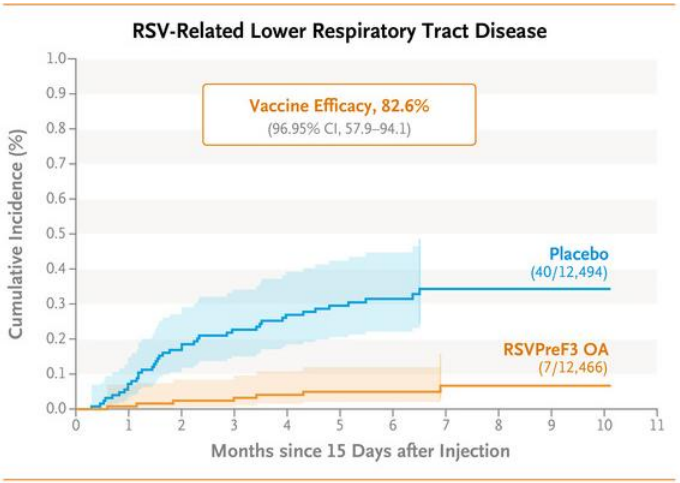


BNT162b2 (Biontech) and mRNA-1273 (Moderna)

- modRNA-based SARS-CoV-2 vaccine (Spike Glycoproteins).

mRNA Vaccines - RSV

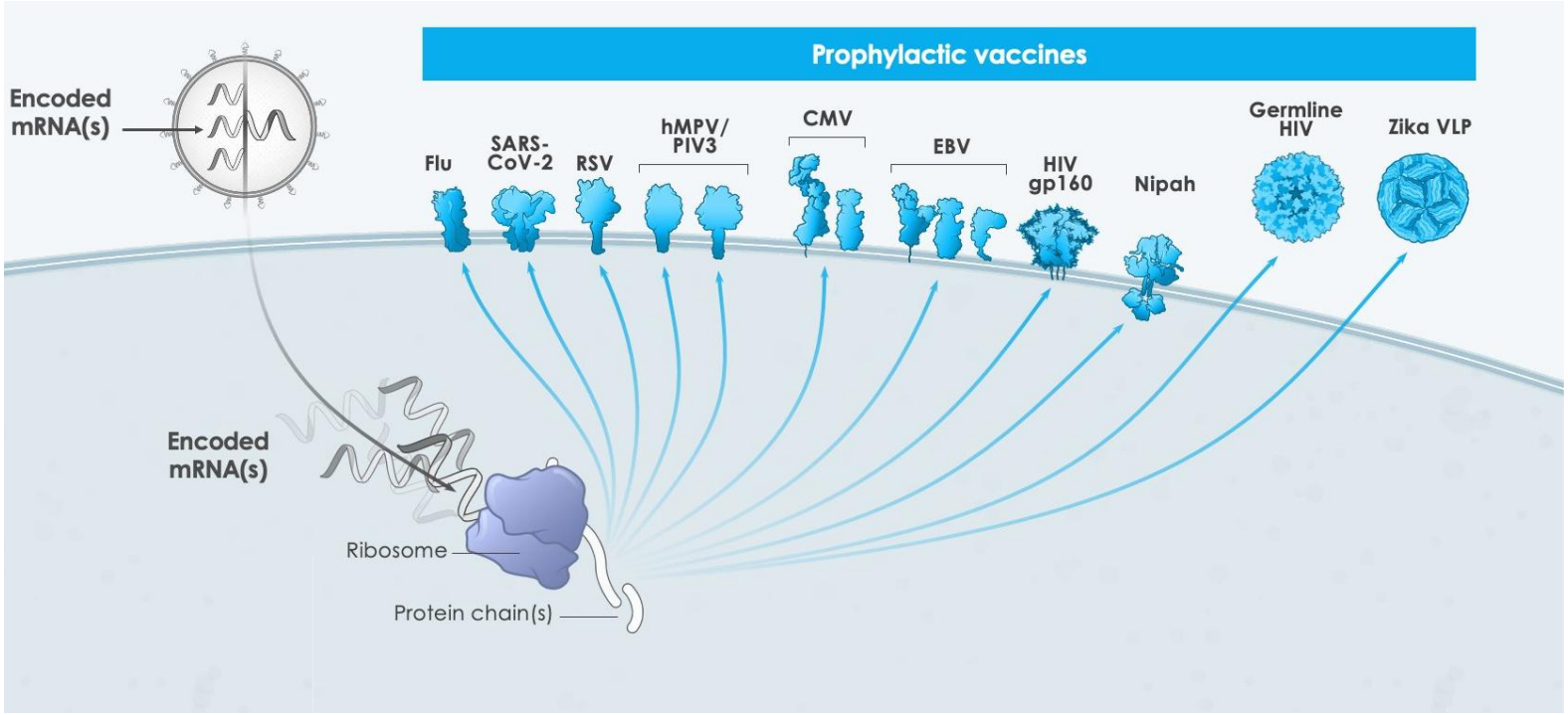




Papi et al. 2023

- Respiratory syncytial virus (RSV)
- FDA approved mRNA vaccine based on prefusion form of F (Key antigen) on May 03, 2023 for people +60
- First attempts since 1966 (formalin-inactivated vaccine)

mRNA Vaccines



Types of vaccines

A Licensed for use

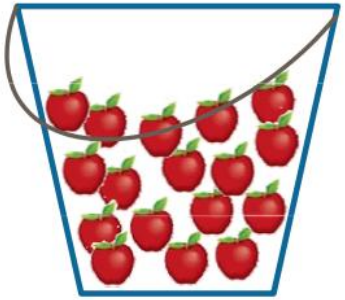
Vaccine type	PAMP	Examples (route if not IM/ID)	Adjuvant	Booster
Live attenuated 	Endogenous 	Measles	None	Yes
		Mumps	None	Yes
		Rubella	None	Yes
		Rotavirus (oral)	None	Yes
		Yellow Fever	None	No
		Chicken pox	None	Yes
		Polio Sabin (oral)	None	Yes
		Live zoster	None	No
		BCG	None	No
		Influenza (nasal: FluMist)	None	Annual
Killed 	Intrinsic 	Whole cell pertussis	None	Yes
		Polio Salk	None	Yes
Split 	Intrinsic 	Seasonal influenza	None	Annual
		Fluad for > 65 yr.	MF59	Annual

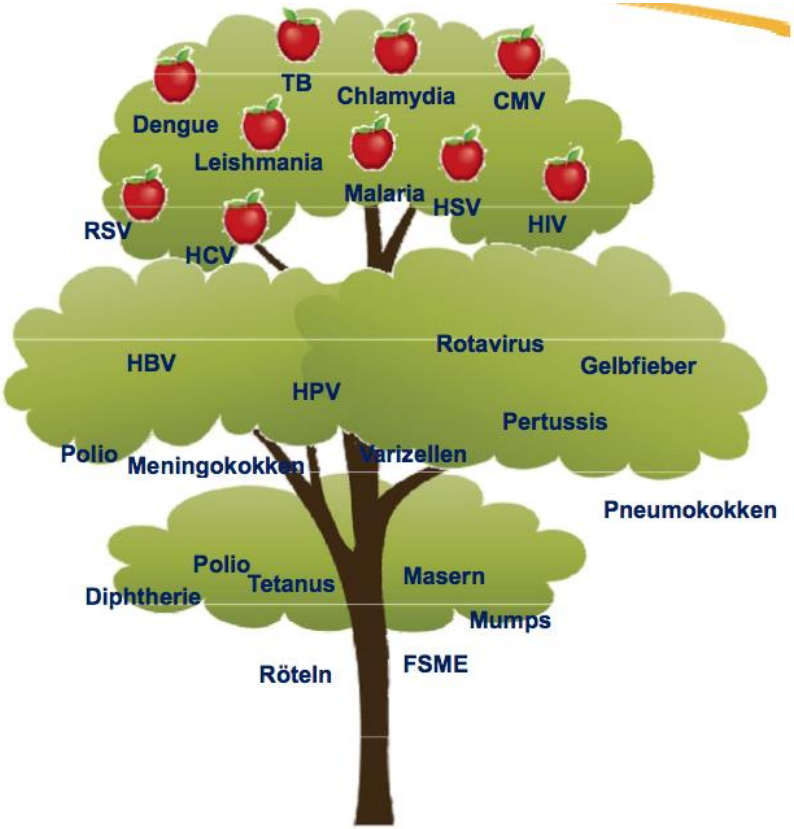
A Licensed for use

Vaccine type	PAMP	Examples (route if not IM/ID)	Adjuvant	Booster
Virus like particles 	Incorporated[a]	HPV Guardasil 9	Alum	Yes
		HPV Cervarix	AS04	Yes
Toxoid 	None	Diphtheria	Alum	Yes
		Tetanus	Alum	Yes
Recombinant subunit 	None	Hep A Havrix	Alum	Yes
		Hep A Vaqta	Alum	Yes
		Hep B Engerix-B	Alum	Yes
		Hep B Recombivax	Alum	Yes
		HepA/Hep B Twinrix	Alum	Yes
		Hep B Heplisav-B	CpG	Yes
		Acellular pertussis	Alum	Yes
		Zoster Shingrix	AS01B	Yes
		Influenza Flublock	None	Annual
Conjugate 	None	MenB Bexsero	Alum	Yes
		MenB Trumenba	Alum	Yes
		Pneumococcal Prevnar 13	Alum	Yes
		HiB	Alum	Yes
Polysaccharide 	None	Pneumococcal polysaccharide PPSV23	None	Yes

https://individuelle-impfentscheidung.de/standpunkte/podcasts.html

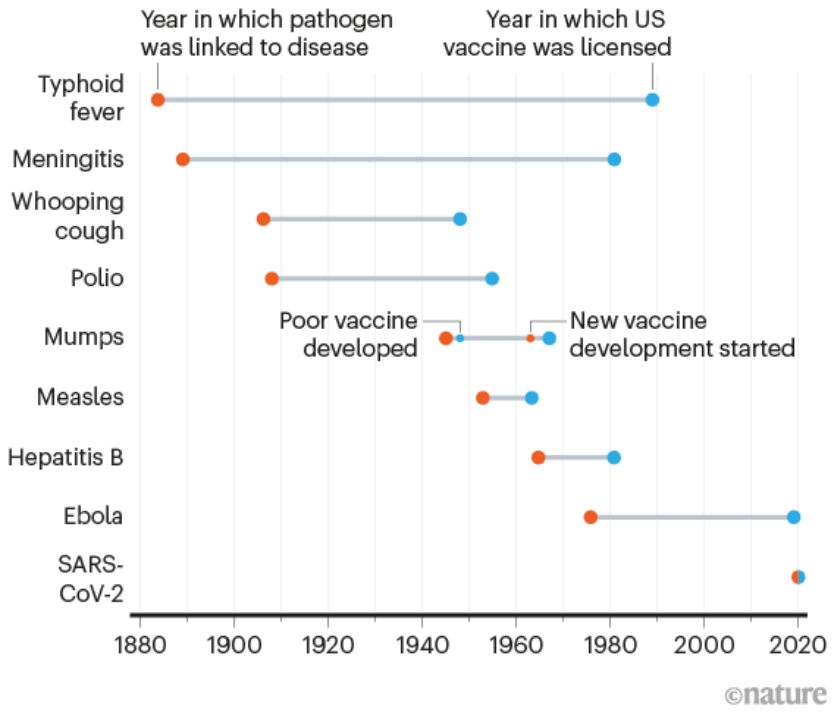
Vaccine developement

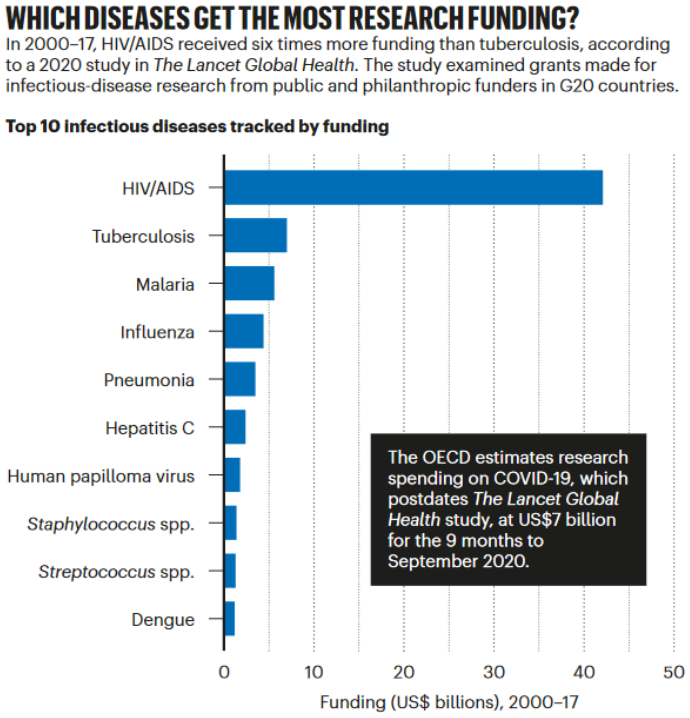




- Vaccines for approximately 30 pathogens available

Vaccine developement



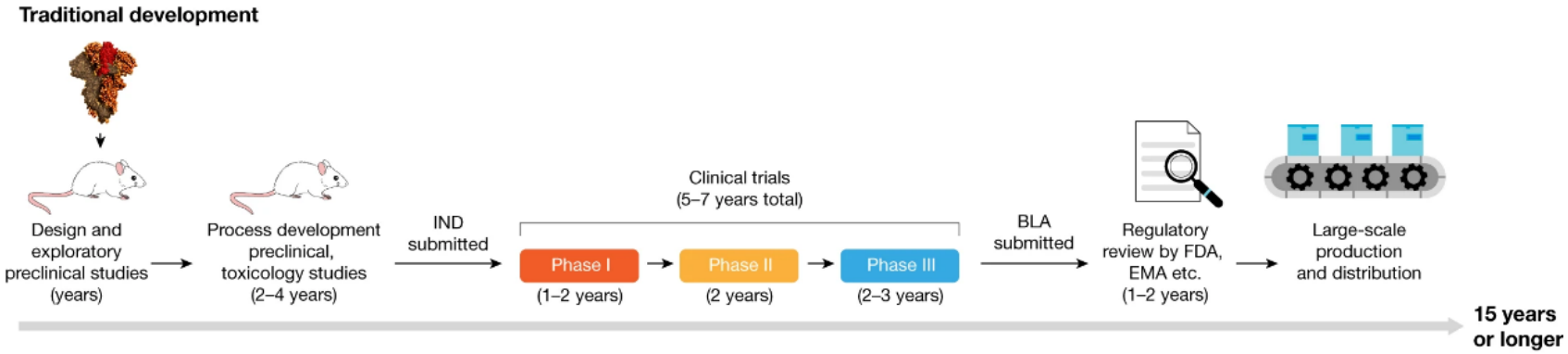


Vaccine developement

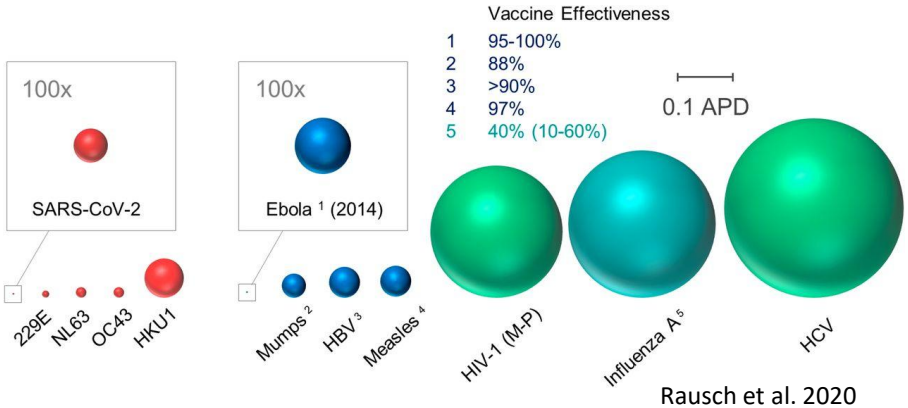
Requirements of an effective vaccine:

- Vaccinated individual must be protected against disease caused by a virulent form of the specific pathogen
  - Just getting 'a response' is not enough (e.g. producing antibodies)

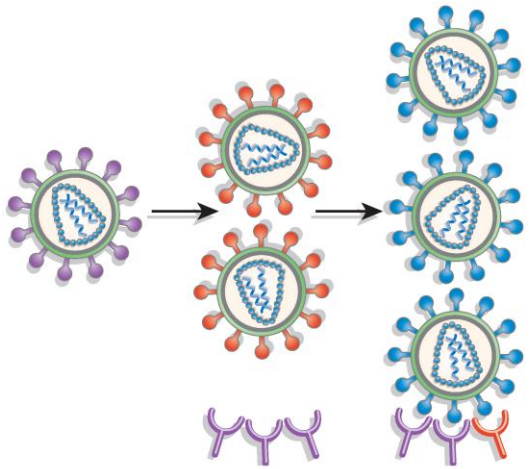
  - Safety: no disease, minimal side effects
  - Protection must be long-lasting
  - Genetic stability
  - Ideally: Low cost, easy to store/deliver (oral vs. needle)



Vaccine development - Challenges



Rausch et al. 2020



High antigenic variability (e.g. HIV, HCV)

HIV Vaccine trials

Vaccine	Trial	1998 – 2001	2002 – 2005	2006 – 2009	2010 – 2013	2014 – 2017	2018 – 2021
Bivalent gp120	VAX 004: AIDSVAX B/B in alum, US, discordant couples, age 18–60 VAX 003: AIDSVAX B/E in alum, Thailand, IVDU, age 20–60						
Ad5, internal proteins	HVTN 504 (STEP): US, MSM, age 18–45 HVTN 503 (Phambili): RSA, heterosexual, age 18–35				STOP		
Canarypox/ bivalent gp120	RV144: ALVAC vCP1521-AIDSVAX B/E, Thailand, community-based, age 18–30					31.2% protection	
DNA/Ad5, internal proteins + Env	HVTN 505: US, MSM, TGSM, age 18–50					STOP	
Canarypox/ bivalent gp120	HVTN 702 (P5): ALVAC vCP2438 – bivalent clade C gp120, RSA, heterosexual, age 18–35						
Ad26 (mosaic)/ trimeric gp140	HVTN 705/HPX2008, 4 mosaic sequences – clade C gp140, Sub-Saharan African women, age 18–35						

Robinson 2018

LATEST NEWS

Janssen and Global Partners to Discontinue Phase 3 Mosaico HIV Vaccine Clinical Trial

Independent, scheduled review of Phase 3 Mosaico study finds investigational vaccine regimen lacks efficacy in preventing HIV

Vaccine development - Challenges

Correlates of protection

TABLE 2. Quantitative correlates and surrogates of protection after vaccination

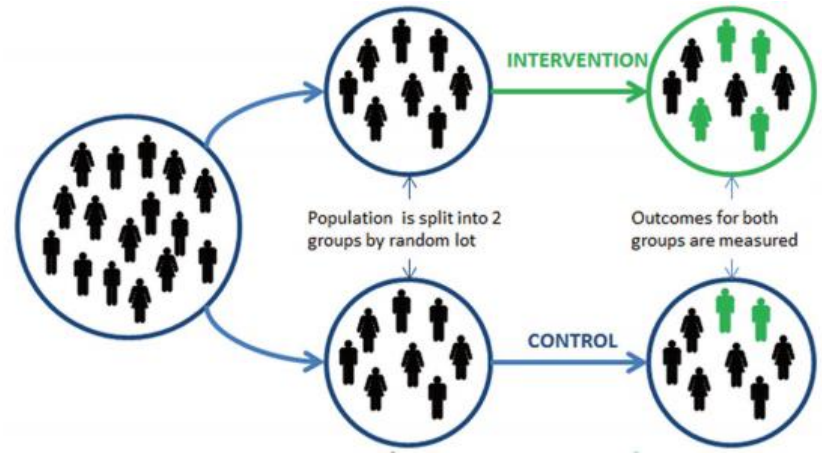
Vaccine	Test	Level required
Anthrax	Toxin neutralization	1,000 IU/ml
Diphtheria	Toxin neutralization	0.01–0.1 IU/ml
Hepatitis A	ELISA	10 mIU/ml
Hepatitis B	ELISA	10 mIU/ml
Hib polysaccharides	ELISA	1 μg/ml
Hib conjugate	ELISA	0.15 μg/ml
Human papillomavirus	ELISA	ND[b]
Influenza	HAI	1/40 dilution
Japanese encephalitis	Neutralization	1/10 dilution
Lyme disease	ELISA	1,100 EIA U/ml
Measles	Microneutralization	120 mIU/ml
Meningococcal	Bactericidal	1/4 (human complement)
Mumps	Neutralization?	ND
Pertussis	ELISA (toxin)	5 units
Pneumococcus	ELISA; opsonophagocytosis	0.20–0.35 μg/ml (for children); 1/8 dilution
Polio	Neutralization	1/4–1/8 dilution
Rabies	Neutralization	0.5 IU/ml
Rotavirus	Serum IgA	ND
Rubella	Immunoprecipitation	10–15 mIU/ml
Tetanus	Toxin neutralization	0.1 IU/ml
Smallpox	Neutralization	1/20
Tick-borne encephalitis	ELISA	125 IU/ml
Tuberculosis	Interferon	ND
Varicella	FAMA gp ELISA	≥1/64 dilution; ≥5 IU/ml
Yellow fever	Neutralization	1/5
Zoster	$CD4^+$ cell; lymphoproliferation	ND

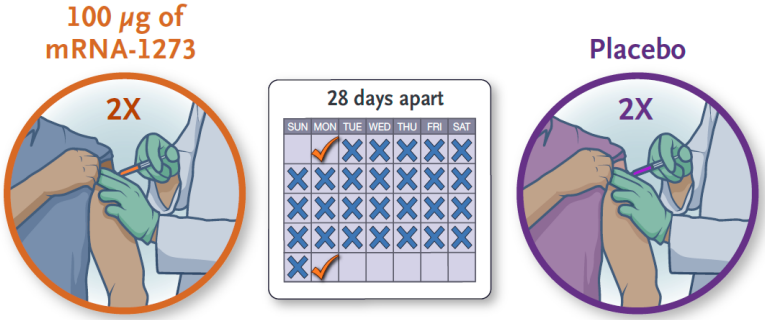
[a] Also see the text.
[b] ND, not defined.

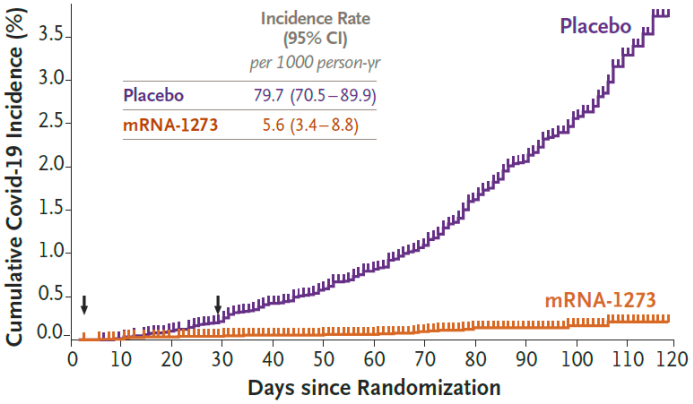
- Immune response must be of adequate strength and quality for efficient protection
- Measurable signs that a person (or other potential host) is immune (i.e. antibodies)
- Without knowing the correlates of immunity, one cannot know exactly what sort of immune response a vaccine would need to stimulate (→ only P3 studies possible)

mRNA-1273 (Moderna)

randomized clinical trial







	mRNA-1273 Vaccine N=14,550	Placebo N=14,598
Symptomatic Covid-19	11	185
Severe Covid-19	0	30

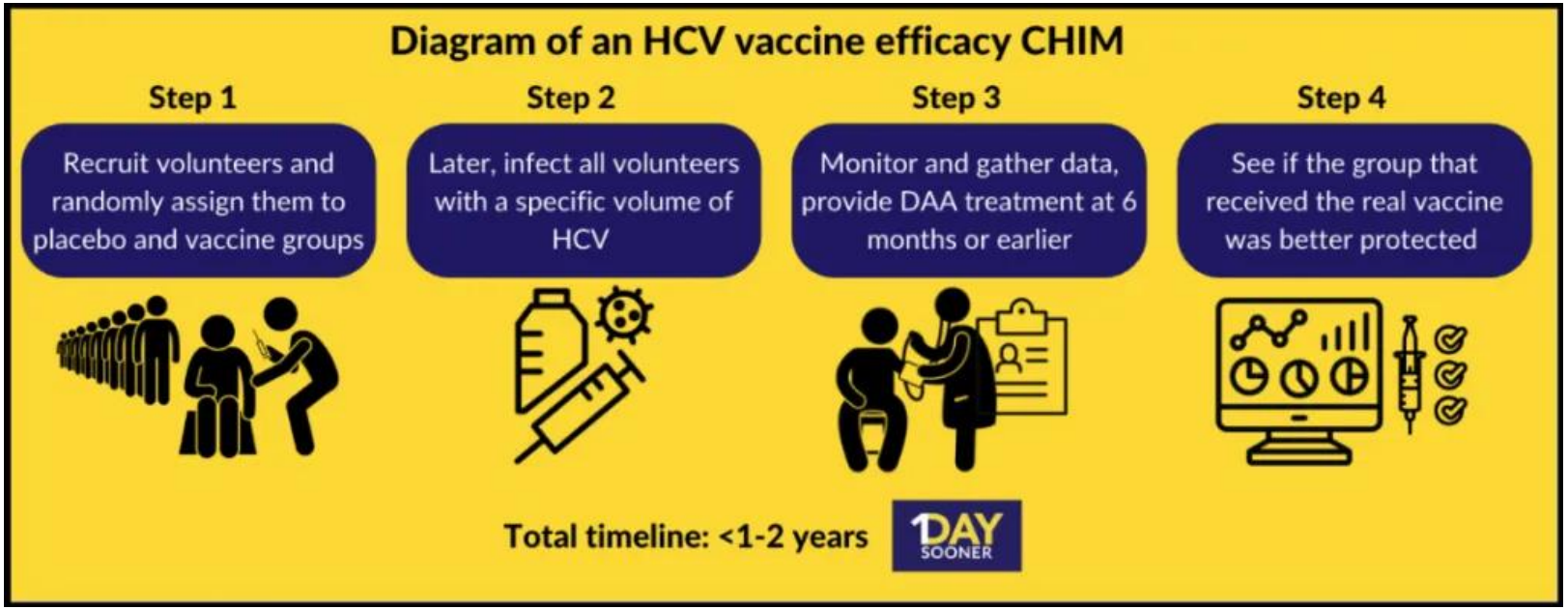
Vaccine efficacy of 94.1% (95% CI, 89.3–96.8%; P<0.001)

CONCLUSIONS

Two doses of a SARS-CoV-2 mRNA-based vaccine were safe and provided 94% efficacy against symptomatic Covid-19 in persons 18 or older.

Vaccine efficacy is generally reported as a relative risk reduction (RRR)

Challenge Study For Hepatitis C?



Antiviral strategies

Hygiene etc.

Vaccines

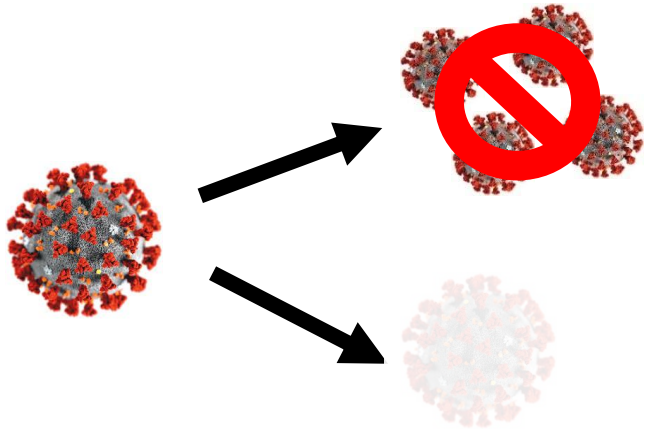
Antiviral drugs

Antiviral drugs

Vaccines can prevent viral diseases. **BUT:** only modest or no therapeutic effect if a person is already infected.

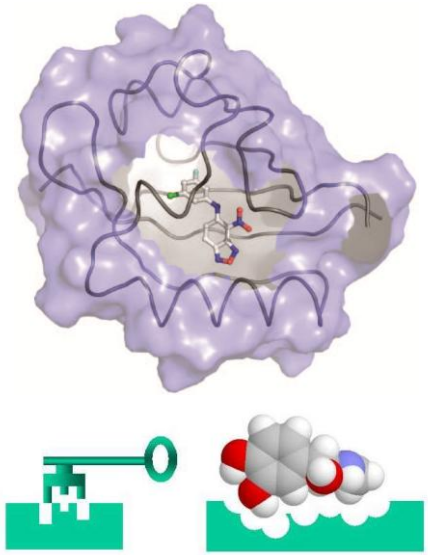
Antivirals are drugs to treat people who have already been infected by a virus.

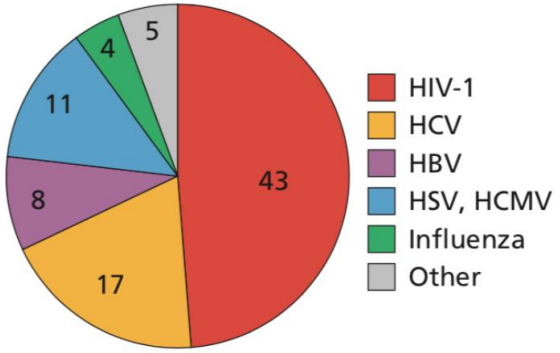
HOWEVER, antiviral substances only inhibit the reproduction of a virus. → virostatic, not virucidal (killing).

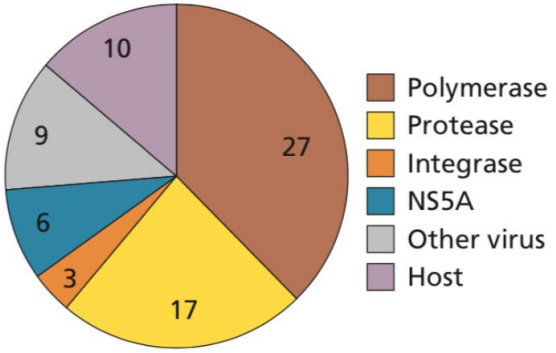


→ Host immune response remains essential.

Antiviral drugs

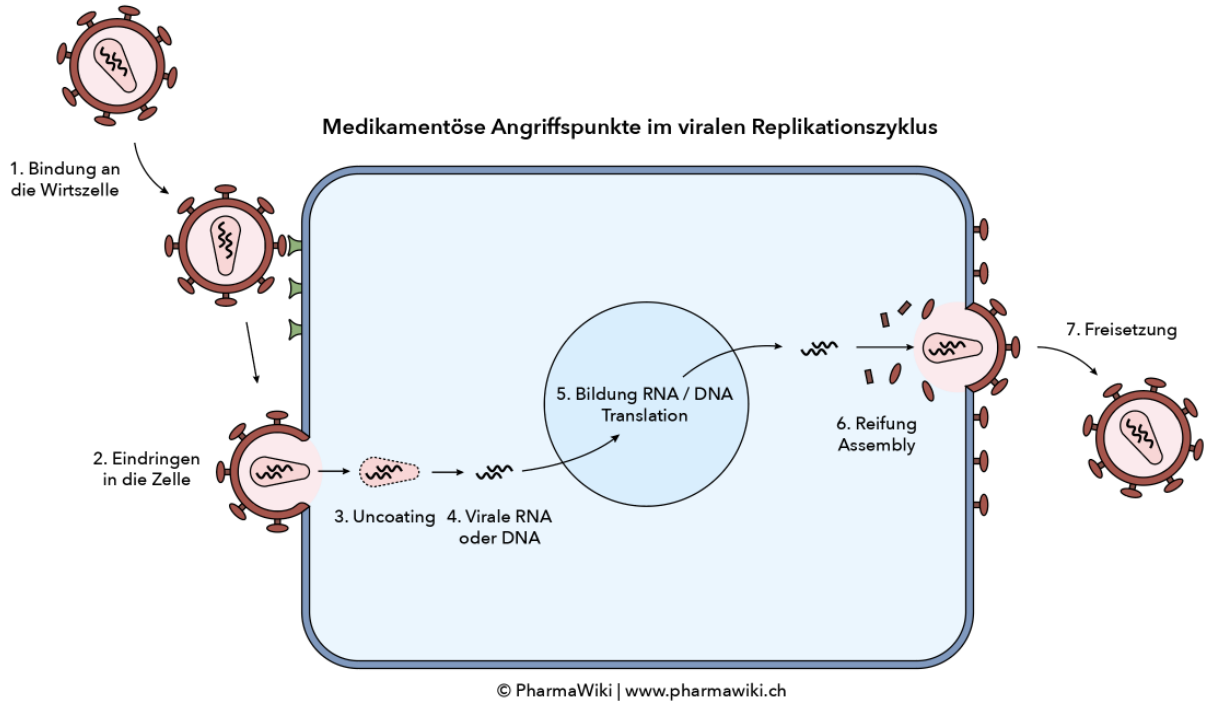






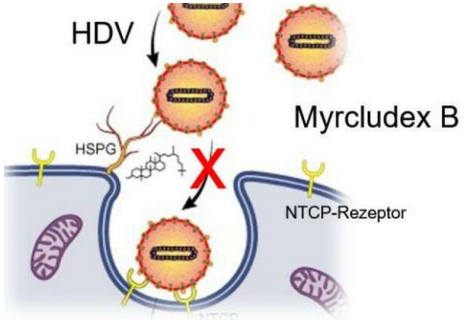
- Small molecule inhibitors for viral / host proteins to perturb essential steps of the viral live cycle
- Frequent targets are viral polymerases and proteases
- Unlike bacteria, there are **no broad-spectrum antivirals**

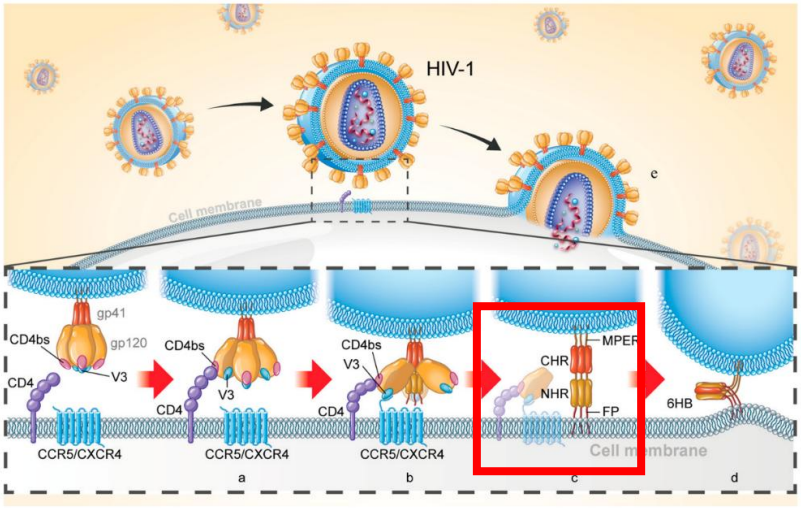
Targets for antiviral drugs



1. Docking, entry into the host cell
2. Viral enzymes (e.g. reverse transcriptase, DNA/RNA polymerases, integrase)
3. Maturation/assembly
4. Release of viral particles
5. (inhibition of cellular proteins)

Fusion/Attachment Inhibitors



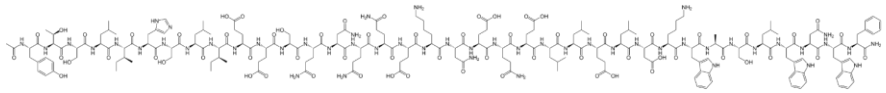


Entry Inhibitor - HDV

- Myrcludex: blocks the entry receptor (sodium/bile acid cotransporter (NTCP))

Attachment-/ Fusion-Inhibitor - HIV

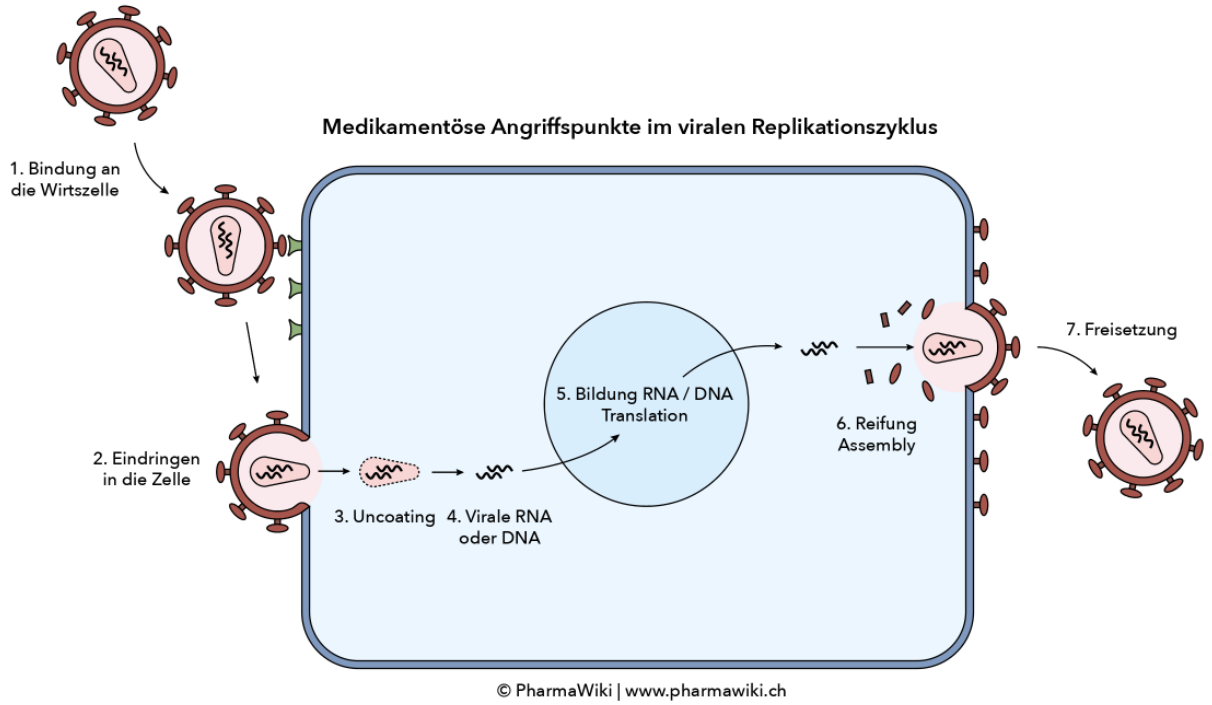
- Fostemsavir, Ibalizumab (mAb): Block virus attachment
- Enfuvirtid: Block virus fusion



Release-Inhibitor - Influenza

- Ion channel inhibitor → Inhibits the release of the viral genome

Targets for antiviral drugs



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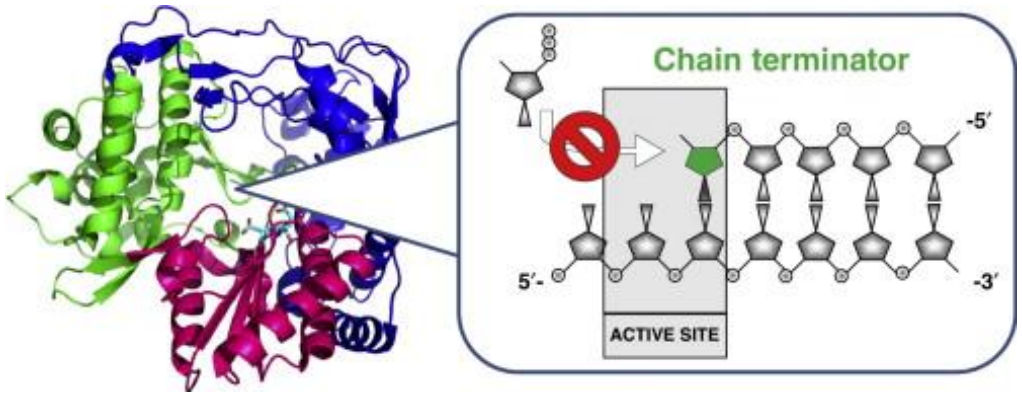
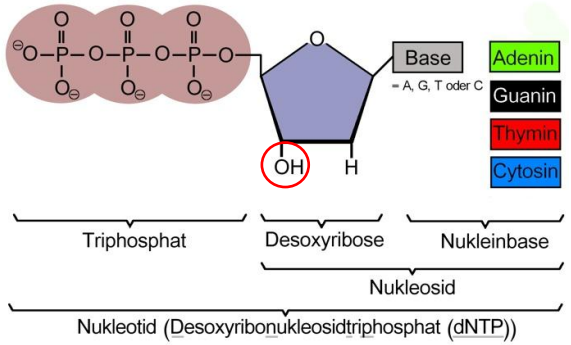
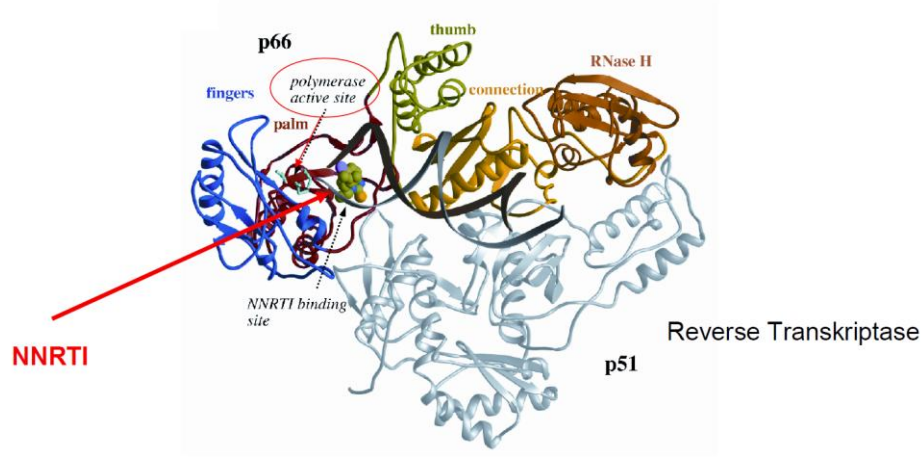
Polymerase inhibitors





- Polymerases need free 3´-hydroxy end to synthesize complementary strand
- Nucleoside/nucleotide analogues chain termination
- Danger: cytotoxicity
- Activation: production of triphosphate by cellular enzymes (prodrug)
  - Aciclovir (HSV)
  - Ganciclovir (CMV)

Non-nucleoside inhibitors



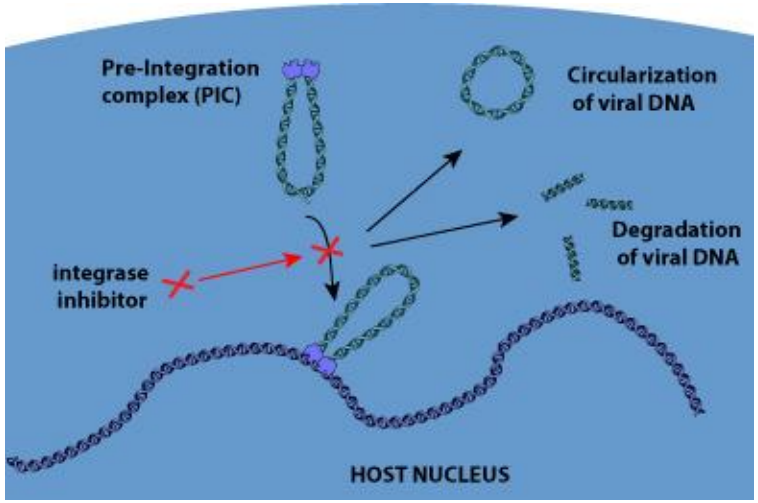
Empfohlene Erstlinientherapie der deutsch-österreichischen HIV-Fachgesellschaft zur Behandlung der HIV-Infektion bei Erwachsenen[*1]

Kombinationspartner 1		Kombinationspartner 2
N(t)RTI Nukleosid-/Nukleotidkombinationen – Tenofovir/Emtricitabin – Abacavir[*5]/Lamivudin	+	NNRTI – Efavirenz[*2] – Nevirapin[*3] Proteasehemmer[*4] – Atazanavir/r – Darunavir/r – Fosamprenavir/r – Lopinavir/r – Saquinavir/r (Alternative, BII) Integrasehemmer – Raltegravir

- Binding to outside the active site (e.g. reverse transcriptase (HIV)).
- No incorporation during nucleic acid synthesis

  → Allosteric inhibition by blocking RT structure
- Non-competitive inhibitors
- Combination with NRTI in HIV

HIV-Integrase

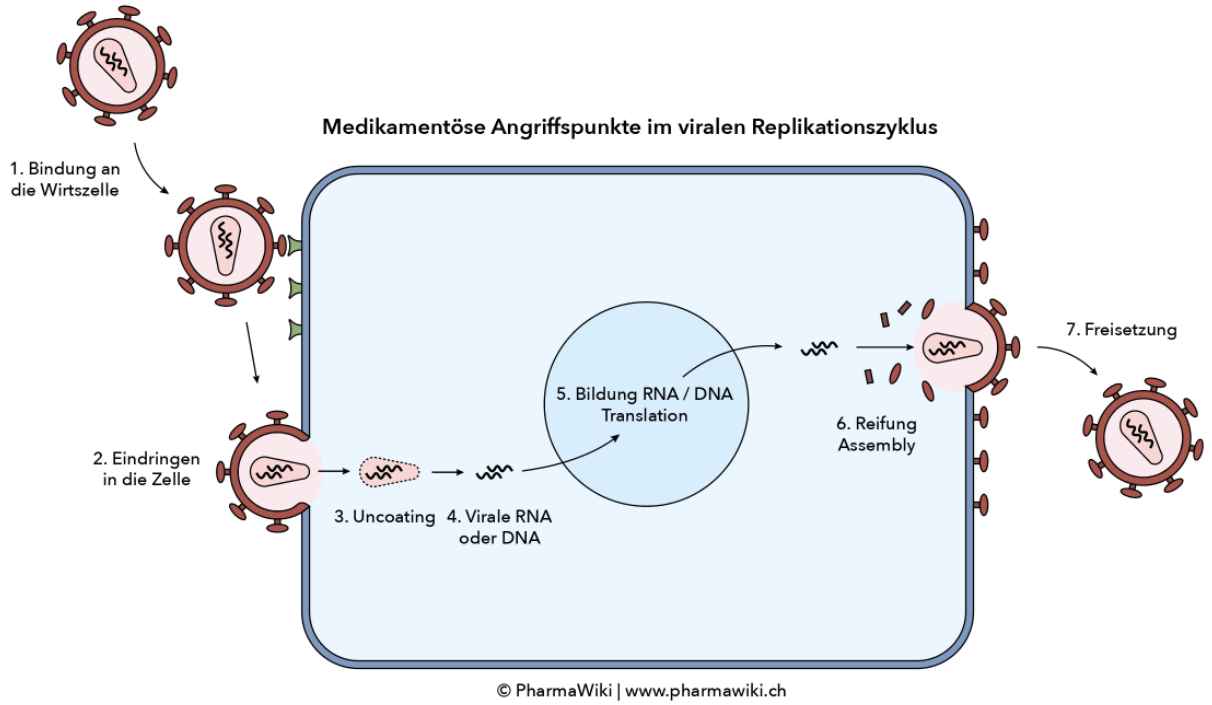


Für die Primärtherapie werden empfohlen:

Eintablettenregime	
Integraseinhibitor-basiert	BIC/TAF/FTC DTG/ABC/3TC DTG/3TC EVG/c/TAF/FTC
NNRTI-basiert	DOR/TDF/3TC RPV/TAF/FTC *oder* RPV/TDF/FTC[2]
PI-basiert	DRV/c/TAF/FTC
Mehrtablettenregime	
Integraseinhibitor-basiert	DTG + TAF/FTC oder DTG + TDF/FTC RAL[3] + ABC/3TC[4] oder RAL + TAF/FTC oder RAL + TDF/FTC
NNRTI-basiert	DOR + TDF/FTC *oder* DOR + TAF/FTC oder DOR + ABC/3TC
PI-basiert	DRV/r + ABC/3TC oder DRV/r + TAF/FTC

- Inhibition of integration of HIV DNA into the genomic DNA of the host cell
- Often rapid and effective reduction of viral load
- High resistance barrier
- Current ART guidelines primarily recommend integrase inhibitors in initial therapy

Targets for antiviral drugs



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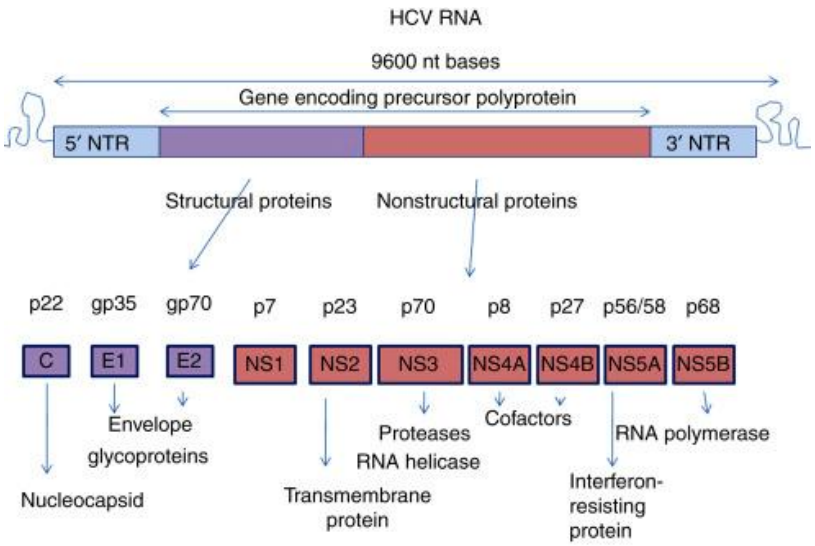
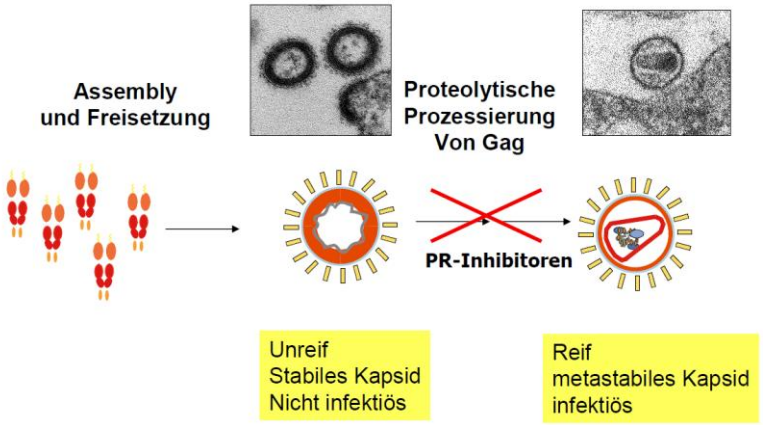
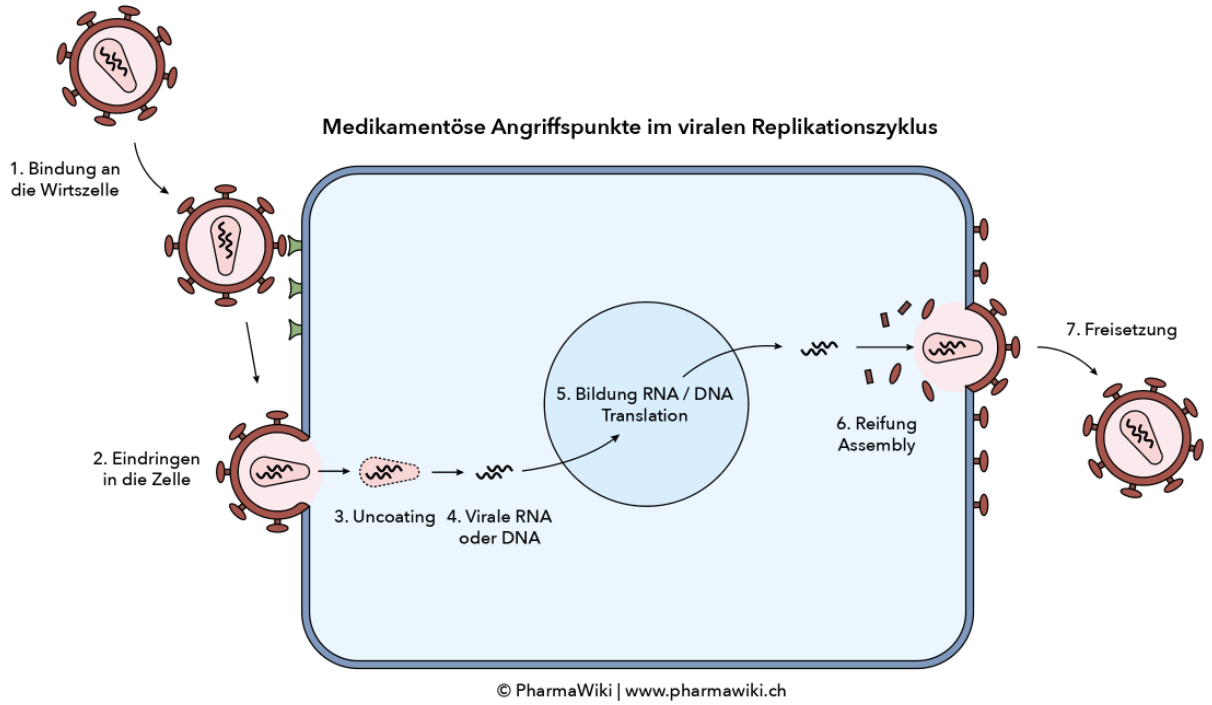
Protease inhibitors





- Virus-derived proteases cut polypeptide precursors into mature enzymes and structural proteins → Essential during viral live cycle
- Binding in the active site (peptide-like structure)
- Eample: HIV, HCV and SARS-CoV-2 (Paxlovid)

Targets for antiviral drugs



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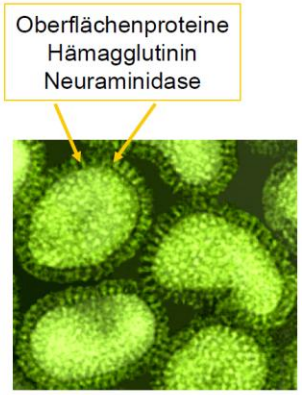
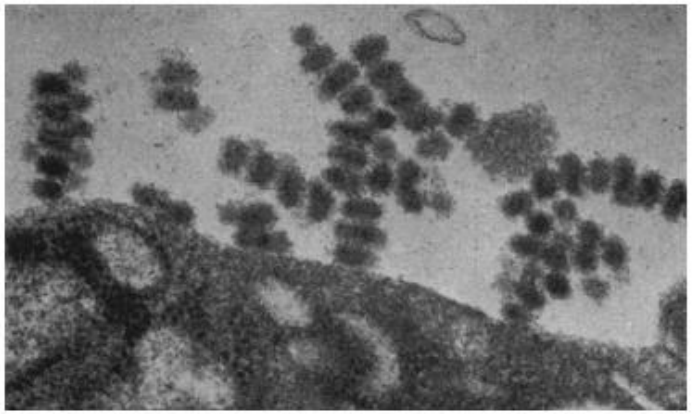
Release Inhibitors



Neuraminidase löst Viren von der Wirtszelle

Oseltamivir
Zanamivir

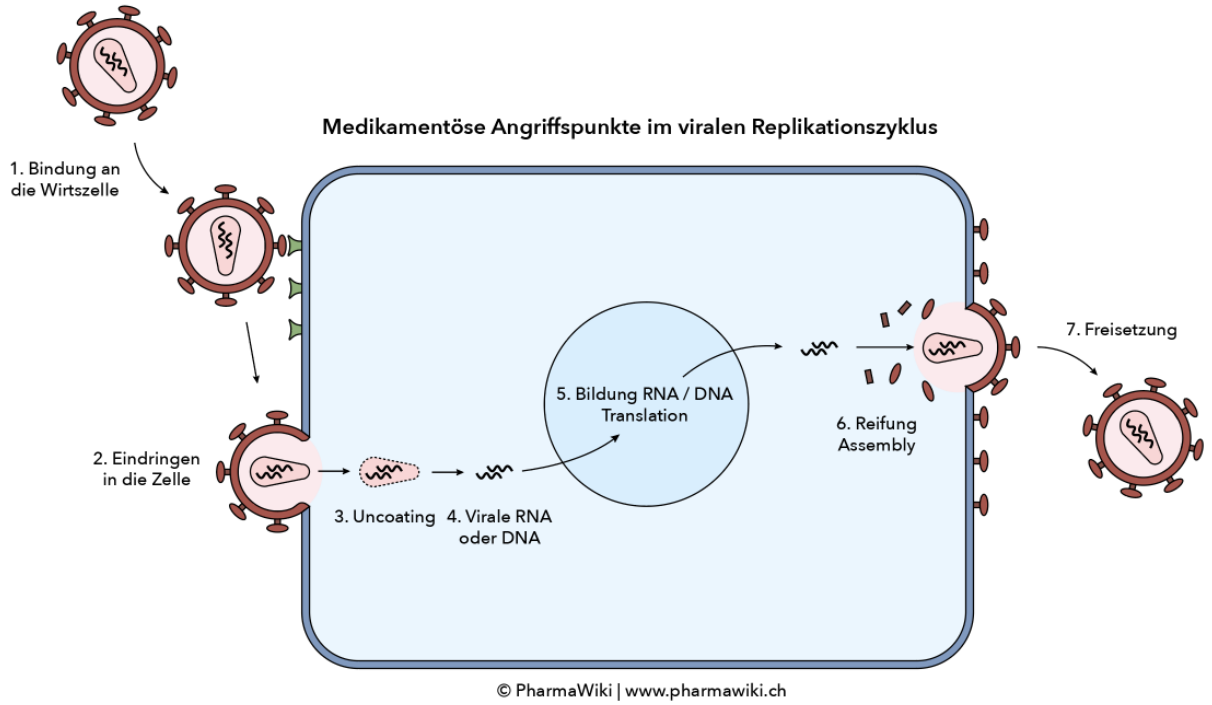
Viren verkleben mit der Zelle und miteinander



Neuraminidase inhibitors block the release of influenza viruses (oseltamivir; zanamivir).

Prophylaxis in high-risk patients → Alleviation of symptoms, shortening of illness duration and reduction of complications

Targets for antiviral drugs



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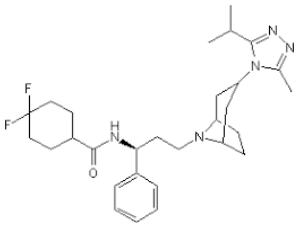
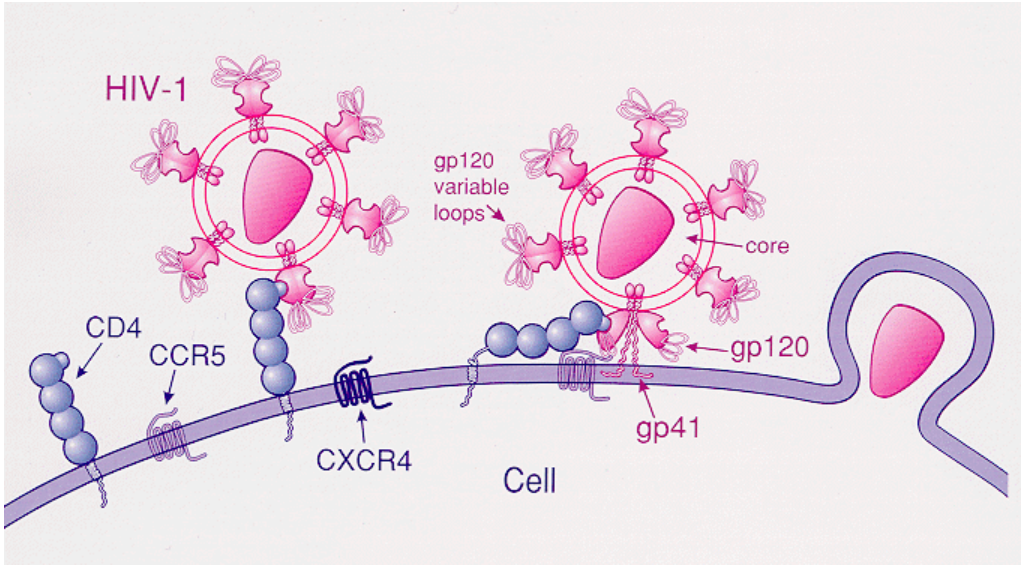
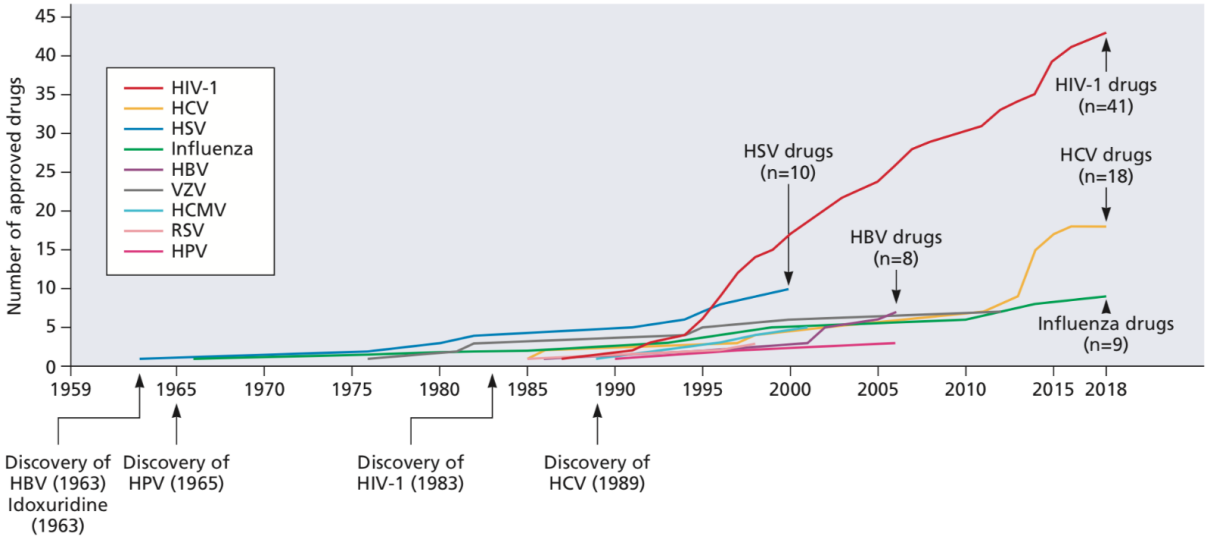
Host-targeting agents





- Maraviroc - HIV entry inhibitor
- Inhibition of fusion by inhibition of the coreceptor CCR5
- Use only with CCR5-tropic HIV-1 (not CXCR4-tropic)
- Combination therapy

Approved antiviral drugs

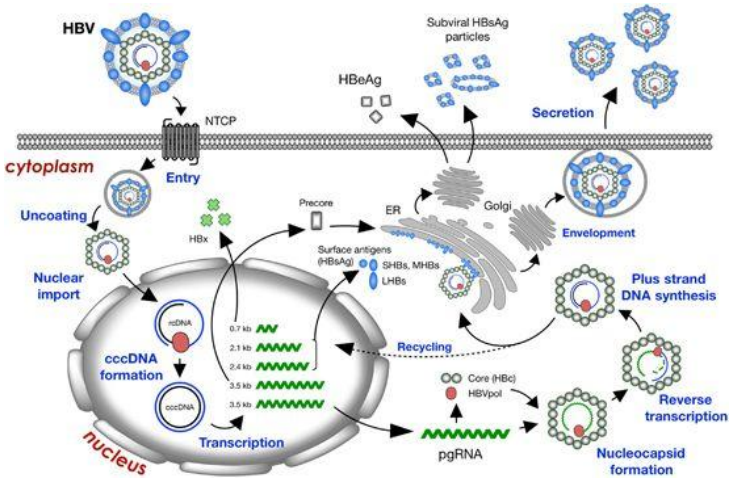


- Only ~100 approved antiviral drugs since 1959
- Most against HIV, HCV, herpesviruses - Persistent infections
- Current antiviral agents do not eliminate non-replicating or latent virus

Why are there so few antiviral drugs?

Compounds interfering with virus growth can adversely affect the host cell

- *Side effects are common (unacceptable)*
- *Every step in viral life cycle engages host functions (selectivity)*



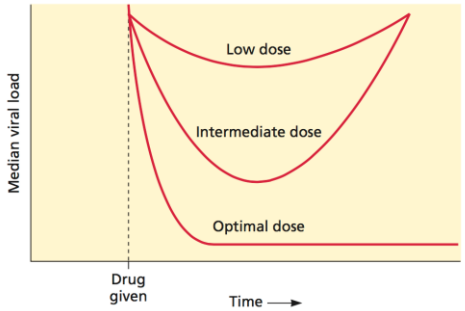
Some medically important viruses can't be propagated, have no animal model, or are dangerous

- *HBV, HPV*
- *Ebola, Lassa*

Why are there so few antiviral drugs?

Compounds must be highly potent

- Partial inhibition is not acceptable - resistant mutants will arise
- Most compounds are **virostatic**, there are no antiviral drugs which are a **virucide**



Acute

- Rhinovirus
- Rotavirus
- Influenza virus

Many **acute infections** are of short duration

- By the time the patient feels ill, it is too late to impact clinical disease
- Lack of rapid diagnostics

Antiviral drugs

Examples of screening compounds

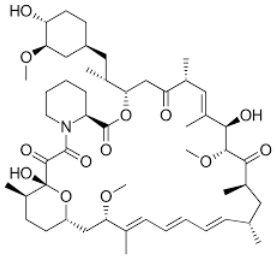
Chemical libraries

Natural products

- Plant extracts
- Microbial fermentations
- Soil Perfusions

Combinatorial chemistry

Rapamycin

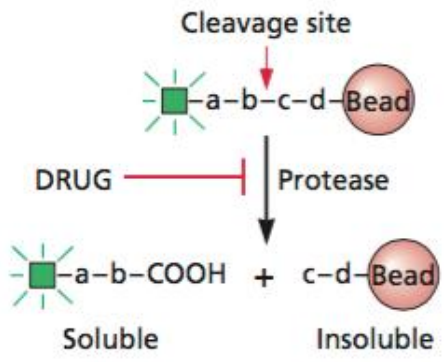


High throughput screening

10,000 compounds/day

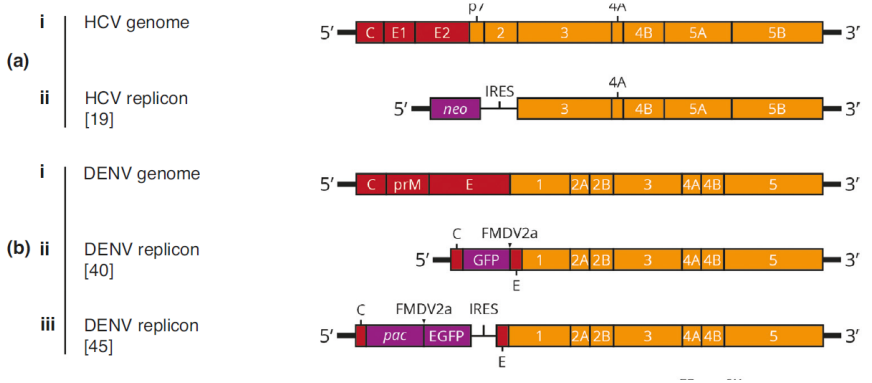
Plate assay – Read outs

Mechanism-Based Screen



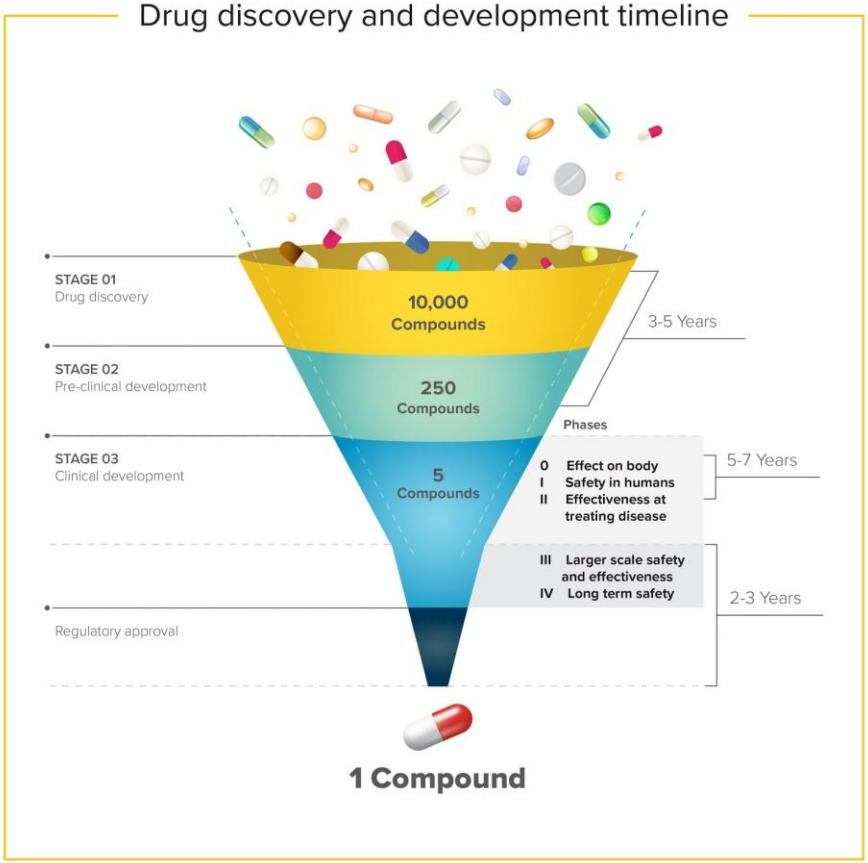
- Inhibition of a specific viral enzyme or molecular interaction
- Low safety requirements

Replicon systems



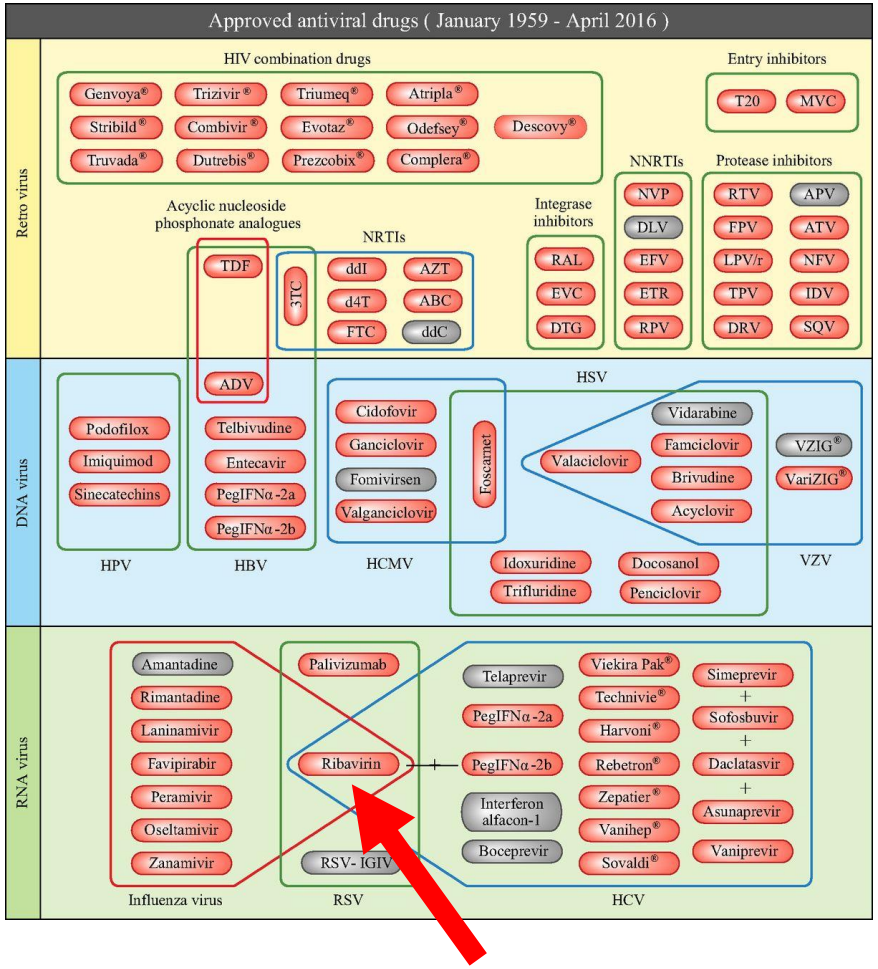
- Subgenomic replicons and mini genome systems
- Self-amplifying recombinant RNA molecules
- Cheap; quick and efficient

The path of drug discovery



- Very low success rate
- Estimated costs ~1 Bio USD
- Time consuming process (10-15 years)

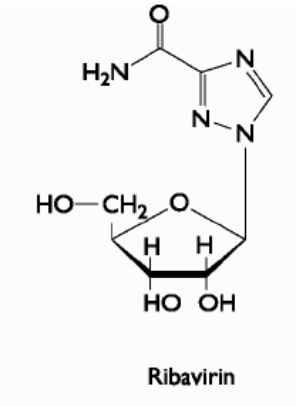
Drug repositioning

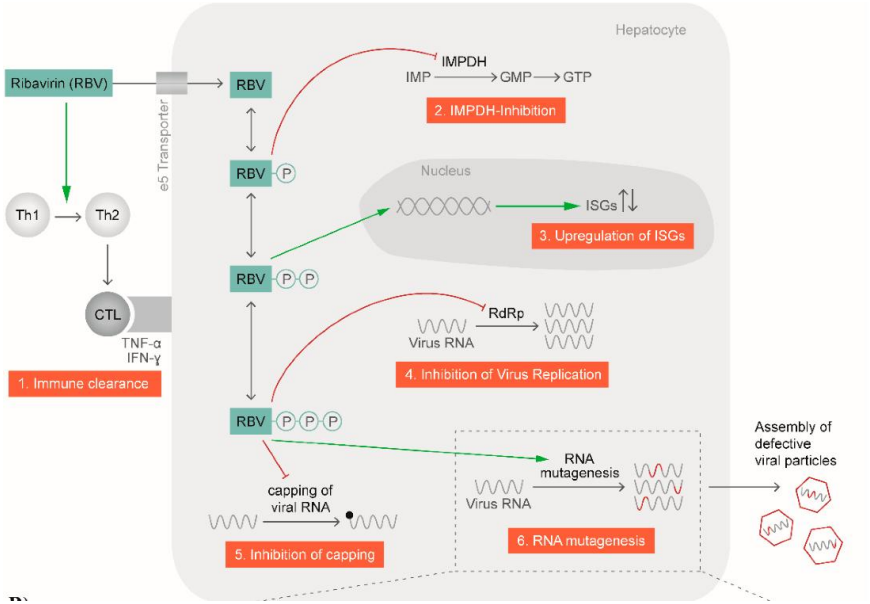


Drug repurposing

Use existing drugs for new therapeutic purposes

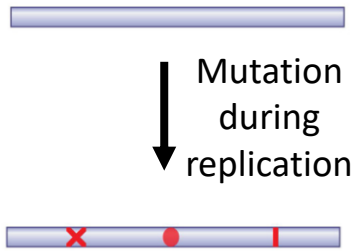
Ribavirin



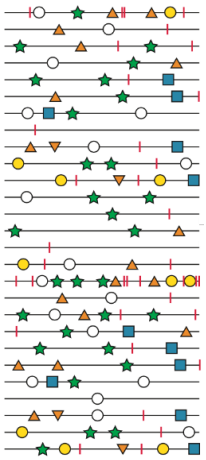


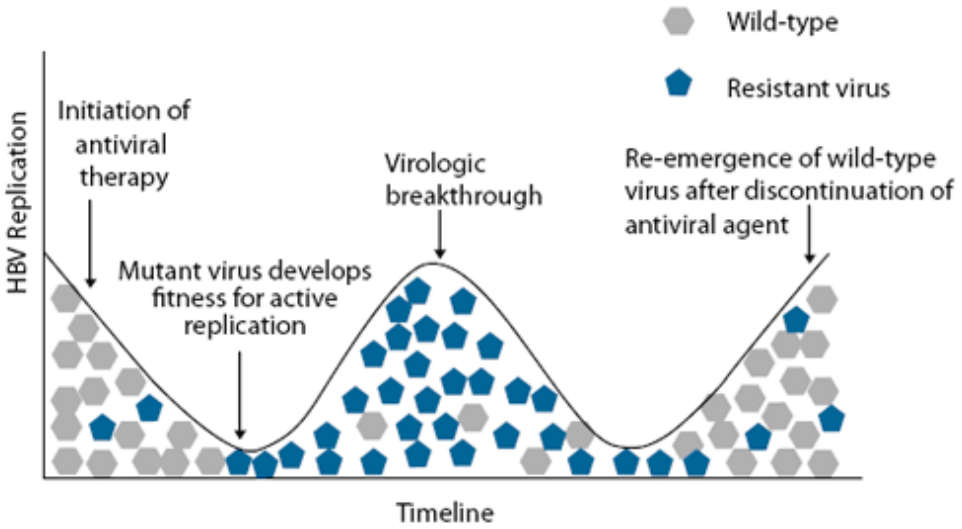
- Guanosine analog
- Relatively unspecific effect (including inhibition of capping, IMPDH inhibition (GTP depletion), RNA mutagenicity)
- Use against various DNA and RNA viruses (e.g. HCV; RSV; Lassa virus; influenza)
    - Currently Off-label use against hepatitis E virus

Drug resistence



heterogeneous
viral populations

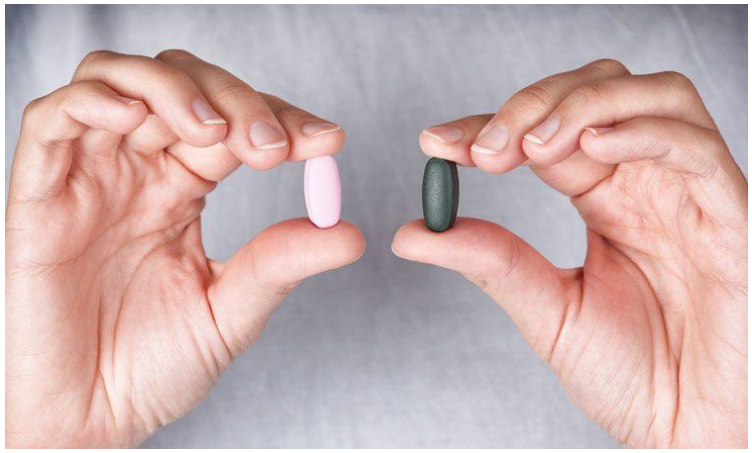


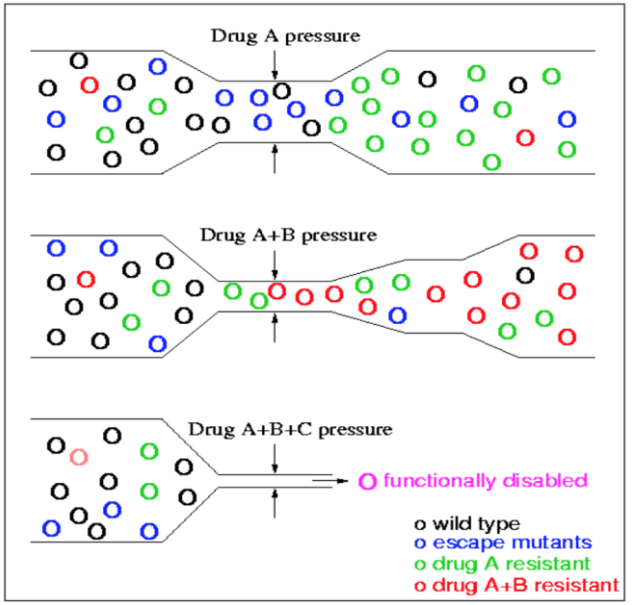


RNA viruses: error prone RNA polymerase → heterogeneous viral populations

DNA viruses: most DNA polymerases have proofreading function → evolve slower

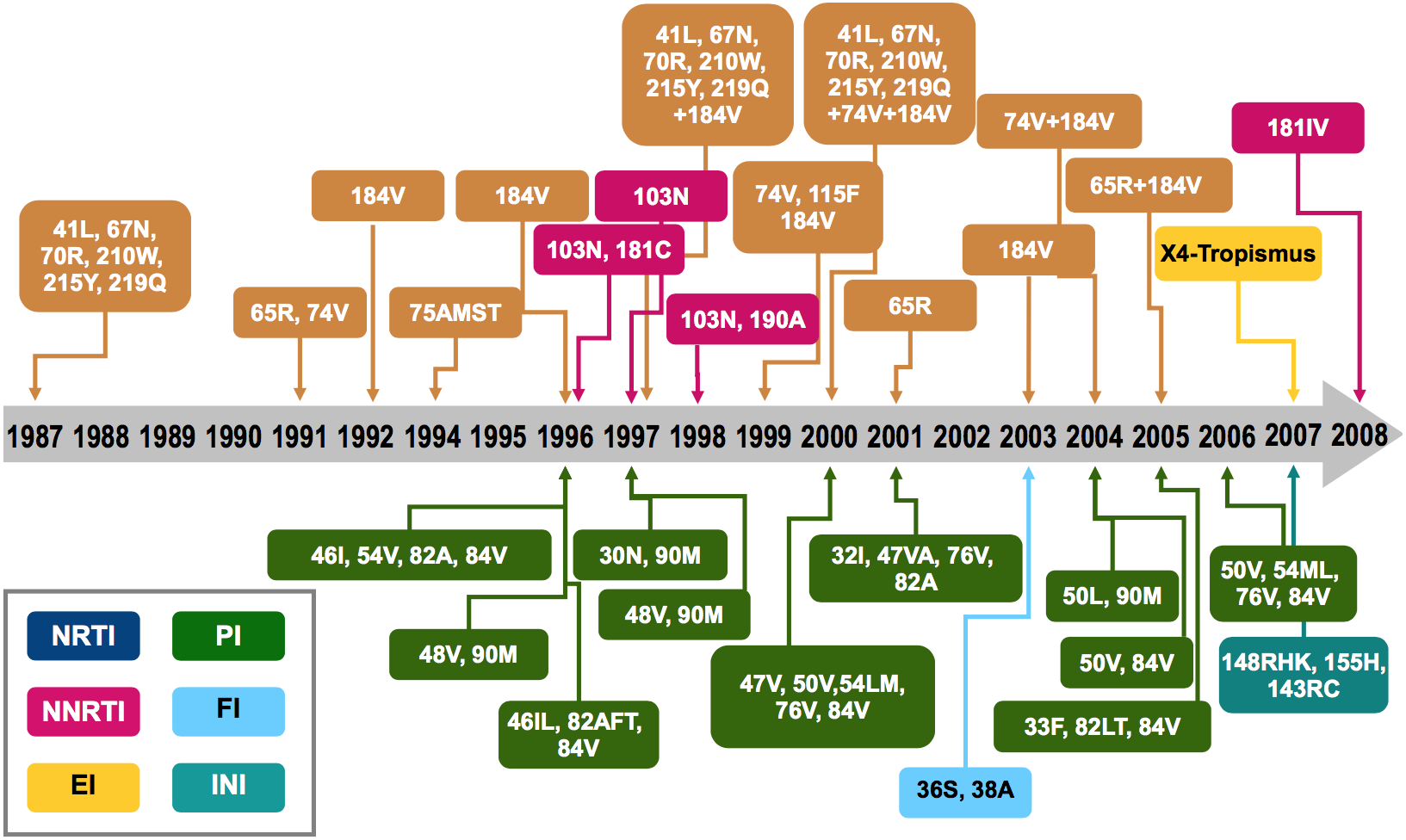
Combination therapy





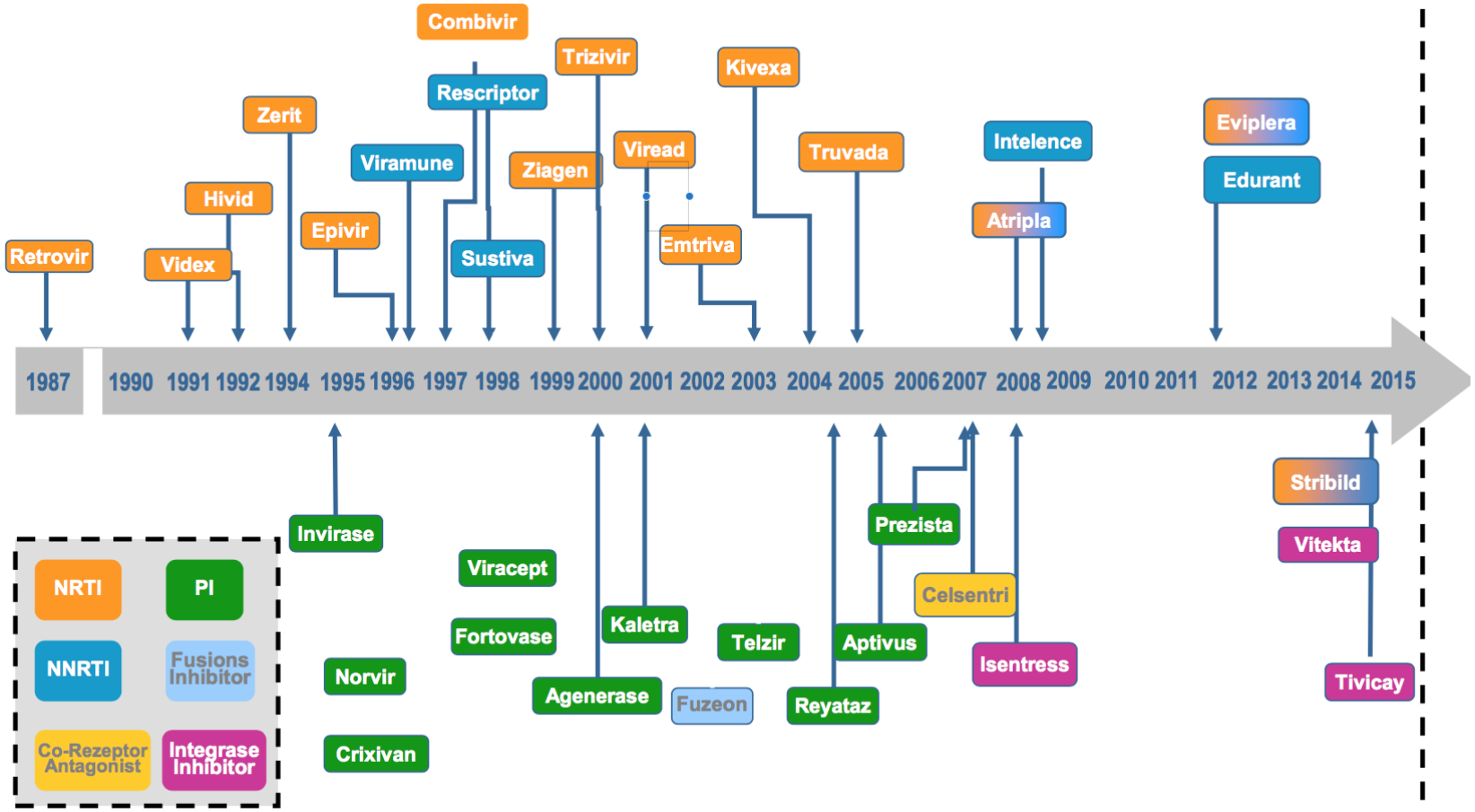
- Stronger selective pressure → Hinders evolution of drug resistances in viruses, bacteria, and cancers

HIV resistence mutations



→ more than 200 resistance conferring mutations

HIV drugs



→ Approximately 30 HIV drugs

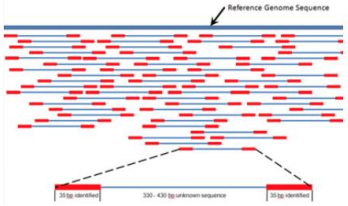
HIV resistence mutations

Blood

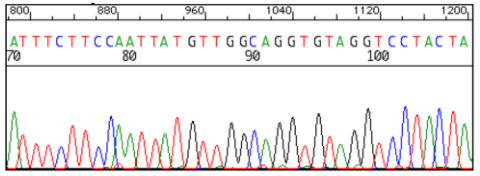
Nucleic acid extraction

gene specific amplification

next generation sequencig



Sanger sequencing



geno2pheno

prediction

interpretation

HIV combination therapy

Combivir® + Crixivan® + Norvir®

Videx® + Zerit® + Viracept®

Combivir® + Norvir® + Agenerase®

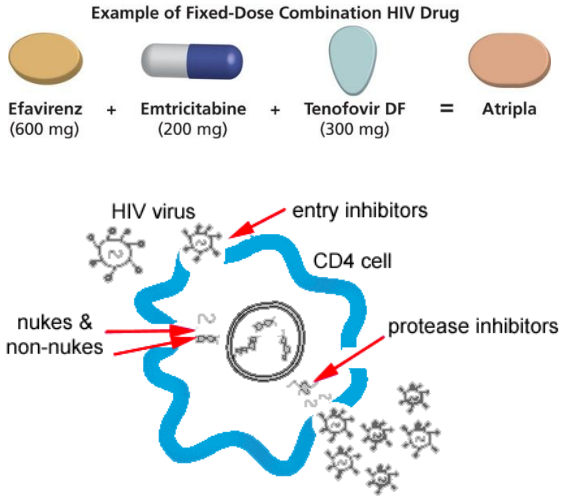
First combination therapies from 1996 (2 RT inhibitors + protease inhibitor)

Initial therapies often with severe side effects

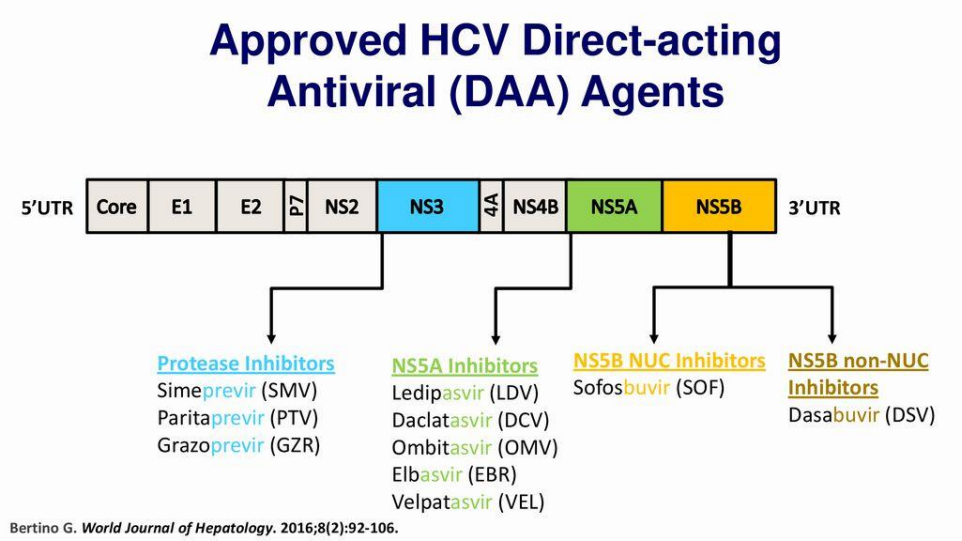
Poor adherence probably most important factor for treatment failure

HIV/HCV therapy

HIV



HCV



Increasingly better HAART approaches minimize adverse drug effects

Almost normal life expectancy with early HAART

Direct-acting antivirals (DAAs)

- 95% of chronic infections can be cured
- First chronic virus infection that can be cured

5g of diamonds

25 1-carat ($1900 each)

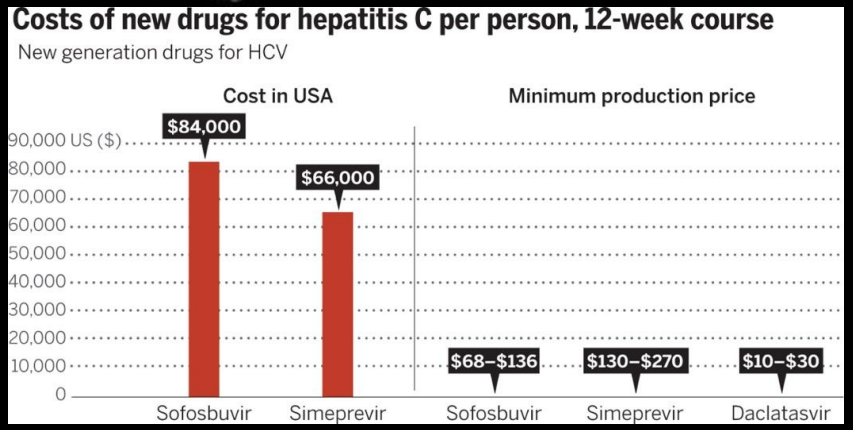
Cost = $48,000

5g of daclatasvir

12 weeks of treatment, 60mg/day

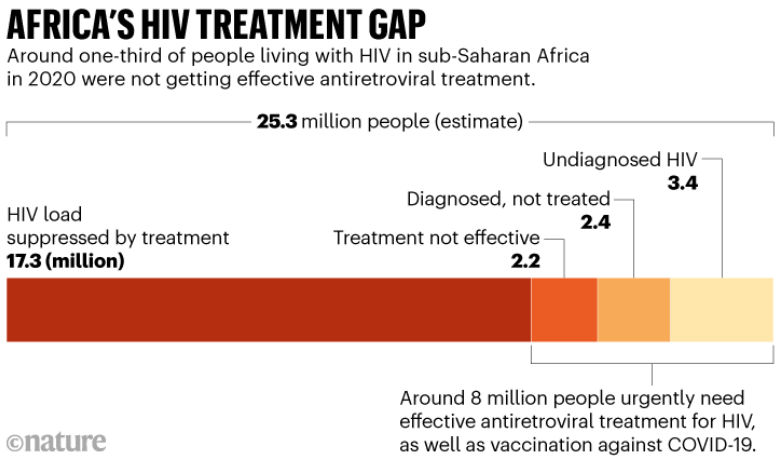
Cost = $63,000 (US price)

Drug	U.S. Patent Expiration	E.U. Patent Expiration
Sovaldi® (sofosbuvir)	2029	2028
Harvoni® (sofosbuvir/ledipasvir)	2030	2030
Epclusa® (sofosbuvir/velpatasvir)	2032	2032

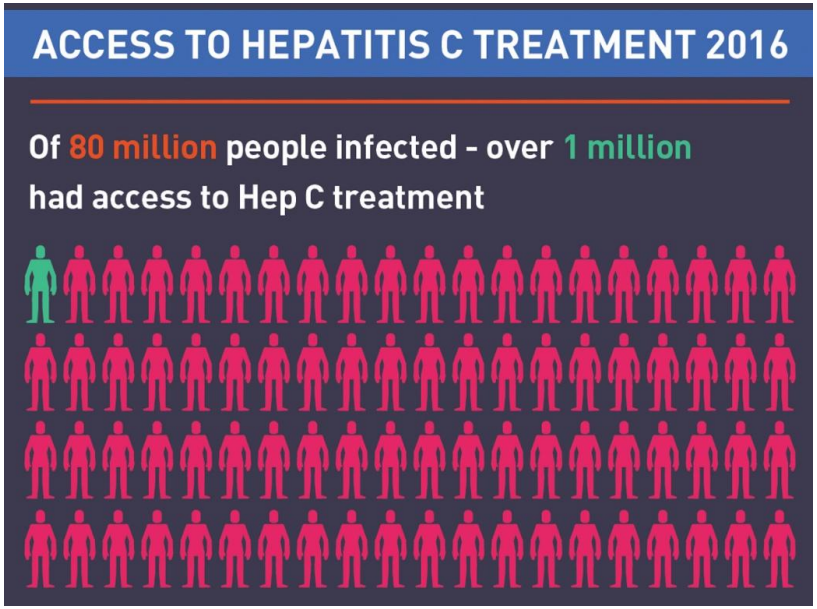


Andrew Hill

HIV/HCV Therapy



Msomi et. al Nature 2021



Summary

Vaccines

- Stimulation of the adaptive immune system to establish immune memory without pathogenic events
- Active and passive vaccines
- Different types of active vaccines (attenuated virus; inactivated virus……)

Antivirals

- Targeting of viral proteins or host factors with small molecules
- Various targets for antiviral drugs (Polymerase; Protease)
- Error-prone viral replication → drug resistance → combination therapy

Thank you for your attention

Molecular & Medical Virology