Infectious diseases

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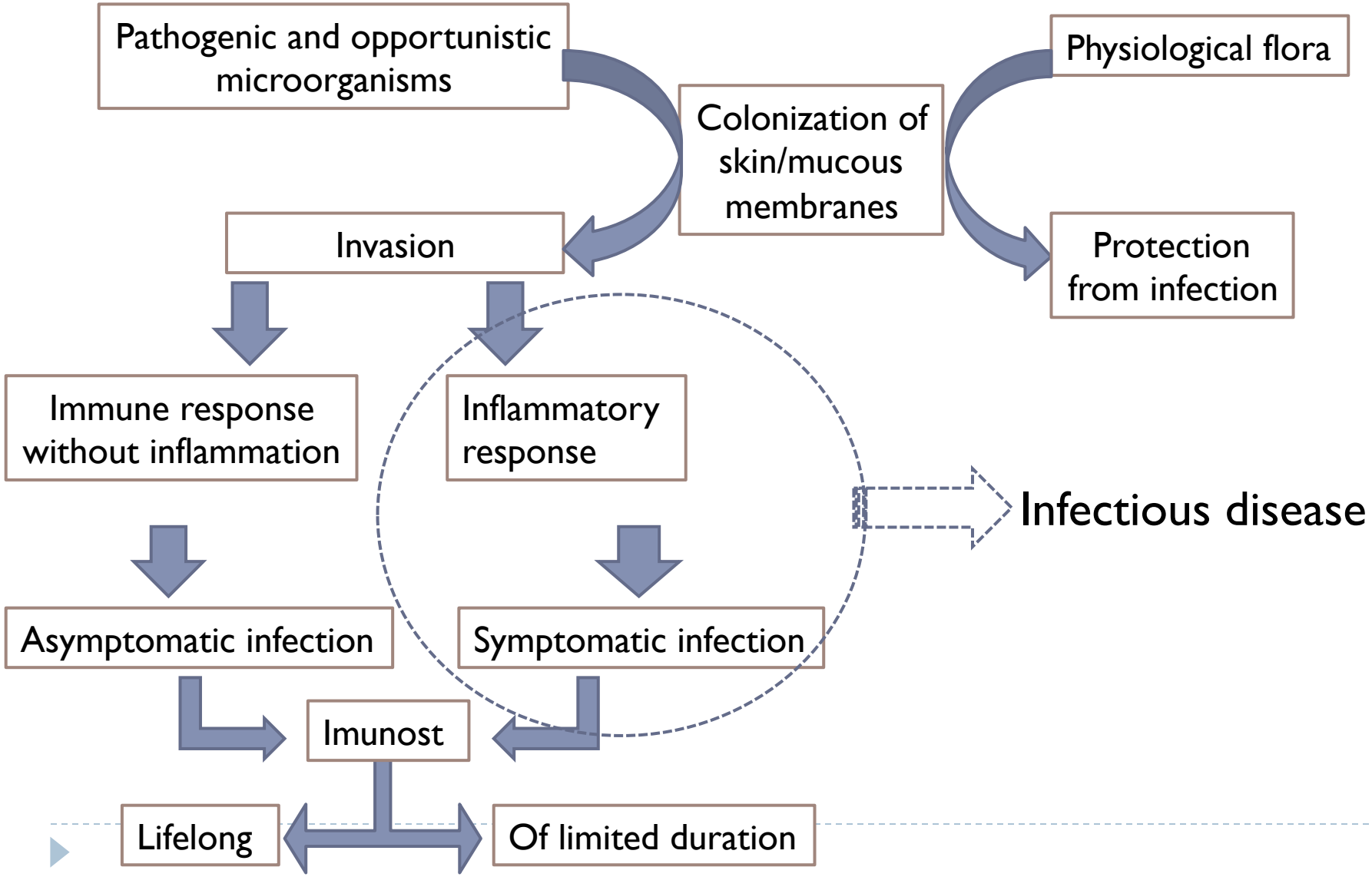
Development of the infectious disease



Pathogenicity (virulence) of the microorganism

Capacity to **invade** and **damage** the host

- **Directly**:
  - by Exotoxins (eg. Cl.difficle toxin, tetanus toxin)
  - by Enzymes (eg. Staphylococcal coagulase)
  - by apoptosis/necrosis-lysis of cells (eg. viruses)

- **Indirectly**: inducing of the inflammatory response
  - by Antigens and Superantigens
    - Septic / toxic shock
    - Cytokine storm

Non-specific host defenses

The **innate immunity**,

independent of the current infection:

- Integrity of the skin and mucous membranes
- Preserved physiological flora

- Phagocytes: neutrophils and macrophages
- NK cells

- Non-specific immunoglobulins (eg. opsonins),
- Interferons

Specific host defenses

Occurs during infection = Adopted immunity

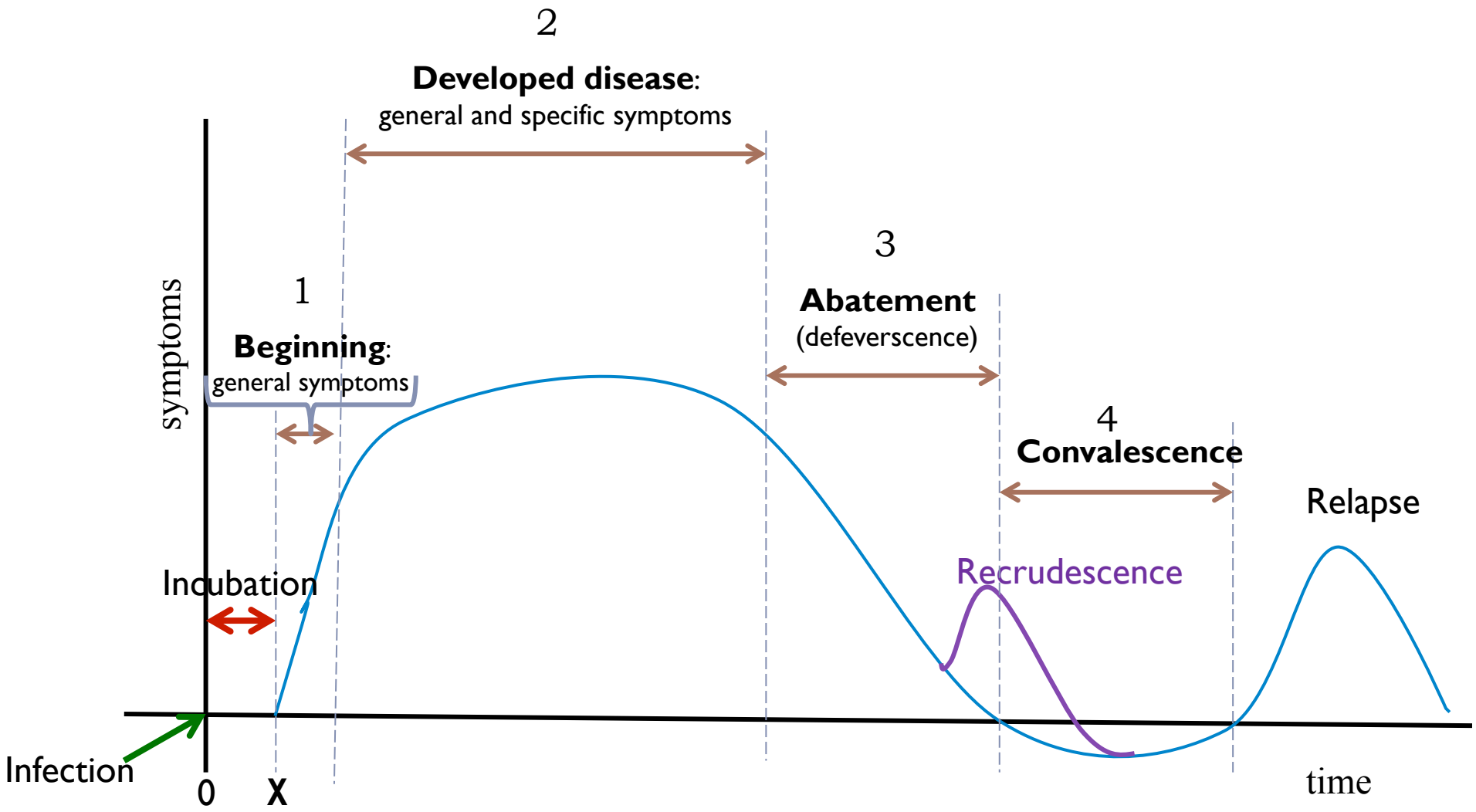
- Finally eliminates current infection
- Protects against further infections

- Specific antibodies (specific B lymphocytes)
  - Facilitate phagocytosis of specific microorganism
  - Neutralize specific toxins

- Specific T cells
  - cytotoxic (Tc): better cytotoxicity than NK cell
  - helper (Th): faster activation of Tc and B lymphocytes

Stages of infectious diseases

- Incubation
  - Time from infection to onset of symptoms
- Symptomatic disease
  - Beginning: general symptoms of infection
  - Developed disease: specific symptoms and signs
  - Abatement of disease (defervescence)
- Convalescence
- Recrudescence and Relapse



Stages of infectious disease

Incubation time

Multiplication and spread of microorganism.

Establishment of the inflammatory response.

- Short: up to 7 days
  - eg. Flu: usually 2-3 (range 1-7 days)
- Medium: 1-2 weeks
  - eg. chickenpox: usually 14 days (range 7-23)
- Long: more than 2 weeks
  - eg. hepatitis B: 1.5 to 6 months

Standardized incubation

- Measels: 11 ± 1 days

General symptoms of infectious diseases

- often the only symptoms at the beginning (first hours - days)
- difficult to set a specific diagnosis

- Fever
- Fatigue and malaise
- Loss of appetite
- Headake
- Myalgias, arthralgias

"Flu like disease"

General pain syndrome

Specific symptoms and signs

Indicate the localization of infection or specific inf. disease

- Abdominal pain, vomiting
- Watery diarrhea

} Gastroenteritis

- Generalized vesicular rash

} Chickenpox (Varicella)

- Icterus
- Enlarged and painful liver

} Hepatitis

Splenomegaly and infectious diseases

- The spleen is part of the RES
- Participates in defense from infection infekcije

Splenomegaly = generalized infection:

- Bacteremic – typhoid fever, brucellosis
- Viremic – infectious mononucleois
- Parasitemic – visceral leishmaniasis

Outcomes of infectious disease

1. Recovery
   A. With eradication of pathogen
   B. Without eradication of pathogen:
      - carrier state (eg. S.typhi), or
      - state of latency (HSV, EBV, HPV) - possible oncogenesis

No inflammation

3. Chronic disease (inflammation)
   A. Progressive - ultimately permanent impairment occur
      - HBV, HCV: liver cirrhosis with / without cancer of the
   B. Persistent - a permanent low grade inflammation
      - without visible damage
      - moguća onkogena transfomacija

5. Smrt

Epidemiological data

Circumstances and risks associated with acquisition infectious diseases

- Host disease that favor infection:
  - multiple myeloma: *S. pneumoniae* and *H. influenzae* sepsis
  - surgery dentures: *S.viridans* endocarditis
- Similarly ill persons from surroundings
- Contact with animals: zoonoses
- Occupational exposure: the veterinary - zoonoses
- Sexual activity: gonorrhea, HIV, HBV
- Travel: tropics (malaria, parasitic diarrhea)
- Consuming of undercooded food: diarrhea
- Vaccination and history of other infectious diseases, ….. etc.

Laboratory evaluation

The attempt to distinguish viral from bacterial infection

- Why? - Fear of delayed antibiotic treatment

- ESR(erythrocyte sedimentation rate):
  - Accelerated in bacterial infection
    - but also in Adenovirus infection
  - At least 2-3 days are required to increase
  - Accelerated also in non-infectious diseases

  - Useful for monitoring therapeutic response

CRP (C-reactive protein)

- Increased in bacterial infection
- The first increase after 8-12 hours diseases
- Also increased in non-infectious diseases with / without fever

- Useful for monitoring therapeutic response

White blood cell (WBC) count and differential cell count (DC)

Increased WBC + Neutrophilia = bacterial infection

- but seen also with Adenovirus infection

Low WBC = viral infection

- but seen also in typhoid fever

DC: left shift (apperance o f non-segment neutrophils)

- More common with bacterial infection
- Ratio n-seg/seg $\geq 0{,}2$ = more likely bacterial inf.
  - even with normal WBC count
  - If WBC count is low = consider serious bacterial infection?

DC: Lymphocytosis

- mostly viral infection
- also seen in pertussis (whooping cough)

DC: Atypical lymphocytes (activated T cells)

- typical for infectious mononucleosis (EBV)
- but also other viral infections, usually less than 5% of WBC

DC: Eosinophilia

- High (> 30%) = tissue parasitic infections
  - trichinosis, pulmonary ascariasis, etc.

Plateletes

- Thrombocytopenia
  - Bacterial sepis (DIC)
  - Also severe viral infections
    - infectious mkononucleois, flu
    - hemorrhagic fevers (dengue, HFRS)
- Thromobocytosis
  - Usualy in convalescence
    - risk of deep vein throbosis

Cerebrospinal fluid (CSF)

	Viral CNS infection	Bacterial CNS infection
Appearance	Clear	Cloudy
Pleocytosis (WBC)	Lymphocytos	Neutrophlia
Proteins	Normal	Increased
Glucose	Normal	Low
Lactate	Normal	Increased
Gram stained sediment	No bacteria	Visible bacteria

Urin analysis

Urinary tract infection (UTI)

- Proteins: increased
- Sediment:
  - Leukocyturia - obligatory
  - Bakteriuria – often present

Other infections (non-UTI)

- Abnormal finding possible
  - mild Febrile albuminuria
  - mild Febrile leukocyturia

Imaging methods

Chest X-ray

- Insight into respiratory infection

Ultrasound

- Solid organs: enlargement, abscesses
- Heart valves: vegetation in endocarditis

CT

- Solid organs of the abdomen, lungs, brain, soft tissues

MR

- Same as with CT + early insight into osteomyelitis

Radionuclide imaging (scintigraphy)

- For osteomyelitis

Detection of infectious agents: direct

- Culture of bacteria and fungi
  - blood, urine, CSF, swabs, biopsy specimens, ….
  - should be obtained before antimicrobial therapy
  - Culture for viruses and parasites are not routine
- Quick imunokromatski tests
  - Influenza: from noses wab
  - Group A streptococci from throat swabs
  - Rotavirus in stool
- PCR for pathogen's DNA or RNA
  - In various specimens containing pathogen

Detection of infectious agents: indirect

Serological tests – detection of specific antibodies (Ab)

- first few days of illness can be negative

Agglutination, et al. (do not separate IgM form IgG)

- Increasingly rarely used
- Paired samples are required

Proving the current infection :

- 4-fold titer increase in two samples, or
- conversion from negative to positive titer

ELISA, IFT, et al.(deteminate IgM and IgG)

- the most commonly ured tests

IgM	IgG	Type of infection	Obtaining of second specimen?
+	neg	Early acute	No*
+	+	Developed acute	No
neg.	+	Previous	No
neg .	neg.	No infection (usualy), or Very early acute infection	No Yes**

* **false positive IgM possible** , for example:
- presence of RF in sera

** **if the same infection remains suspected**

Vaccination and prevention of infectious diseases

Immunisation

Passive: immunization with pre-formed antibodies

- Transplacental transfer of maternal IgG
- Administration of human immunoglobulins
  - human tetanus IgG (HTIG)
- Administration of animal immunoglobulins(serums)
  - botulinum immunoglobulin, anti-viper serum
- Administration of monoclonal antibodies
  - RSV

Active: immunization with antigens = the vaccines

1) Live attenuated microbs:
   - measles, mumps, rubella (MMR), varicella
2) Killed (inactivated) microbs:
   - Intramuscular polio, influenza, hepatitis A
3) Reasorted viraql vaccines ("arteficial virus")
   - genetic rearrangement of different viruses
   - RotaTeq: 4 serotypes of rotavirus

4) Recombinantly derived viral antigens:
   - gene of the vaccine antigen is incorporated into the DNA of yeasts or bacteria
     - HBV, HPV

6) Toxoids
   - Inactivated toxicity, preserved immunogenicity
     - Diphteria, tetanus

8) Purified bacterial antigens (acellular vaccine)
   a) Solitary Ag: *S.pneumoniae* (polysaccharide vaccine)
   b) Multiple Ag: *B.pertussis* (PT, FHA, Pertactin ± Fimbriae)

About polysaccharide vaccines

1. Polysaccharide:

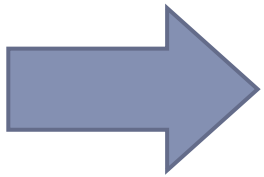
- Good immunogenicity for adults
- Weak immunogenicity for children aged ≤2 years
  - poor activataors of CD4 lymphocyte (Th) in chldren

2. Conjugated poysaccharide:

- poysaccharide + protein (eg. recombinant diphteria toxoid)
- good immunogenicity for childrena (and adults)

General contraindictions for vaccination

- Previous allergy to same vacccine
- Anaphylactic egg allergy, such as urticaria
  - eg: Influenza vaccine
  - Measels and mumps??- not any more
    - Instead on egg, now are produced on chicken fibroblasts culture
- Serious immunodeficiency / immunosupression and pregnacny
  - Zabranjena su živa cjepiva



Serious immunodeficy (contraindications for live vaccines)

- Congenital immunodeficiency
- HIV infection – if in advanced stage
  - otherwise, allowed and recommended
- Lymphoma, leukemia
- Malignancies on therapy
- Corticosteroid therapy: prolonged or high dose
  - > 2 mg/kg/day for more than 2 weeks

About varicella vaccine:

- Cellular immudeficiecy- NO, do no vaccinate
- Hypo/disgamalobulinemija- YES, do vaccinate

Mandatory vaccine in RH 2014- calendar

Vaccine \ Age	Months					Years		Grade of elementary school			Years	
	0	2	3	4	6	2	6	I	VI	VIII	19	60
BCG	BCG											
HIB			Hib	Hib	Hib	Hib						
DI-TE-PER			DTPa	DTPa	DTPa	DTPa	DTPa					
POLIO			IPV	IPV	IPV	IPV		IPV		IPV		
DI-TE								dT		dT	dT	
MO-PA-RU						MPR		MPR				
HEPATITIS B	HBV	HBV			HBV				HBV (3x) x			
ANA-TE												Te

Legend:

BCG: tuberculosis. **Hib**: Hemophilus infuenzae type B. **DTPa**; Diphteria, Tetanus, Pertusis acellular vaccine. **IPV**: Inactivated PolioVirus. **dT**: diphteria and Tetanus. **MPR (MMR)**: Morblili, Parotitis (Mumps), Rubeola. **HBV**: hepatitis B virus. **Te**: tetanus.

x: if not previously vaccinated

Reduceing the number of vaccine doses (punctures)

1 2 3

- Vaccine “3 in 1” (D T Pa)

4 5

- Vaccine “5 in1” (DTPa + IPV+ Hib)

6

- Vaccine “6 in 1” (DTPa + IPV+ Hib + HBV)

Other mandatory vaccination

TETANUS

- For injured (vounded) persons

HEPATITIS B

- Presons in increased risk (health care workers, IV addicts)

RABIES

- Professinal exposure
- Bite by animal that has rabies or is suspected for rabies

- YELLOW FEVER and COLERA, for travellers:
- to a country with these diseases
- to a country that requires immunization against them

Optional, but recommended vaccines

Influenza

- all children and adults, especially those at high risk

S.pneumoniae

- Children – conjugated vaccine
  - all, especially high risk children
- Adults - conjugated and non-conjugated vaccines
  - Those at risk, all aged ≥65 years

Rotavirus

- All children

HPV

- All girls before puberty

Varicella (VZV)

- Persons at risk
- reproductive age women with no history of varicella

Herpes zoster (VZV)

- Persons aged >50 years

TBE- tick borne encepahalitis

- Professional exposure – pre exposure vaccination
  - Forestworkers, hunters, nature lovers
- Following tick bite in an endemic area- post exposure vacc.

A and C meningococcus (polisaccharide non conjugated)

- Travel to Sub-Saharan meningococcal belt
- The occurrence of disease in a collective (military barracks, sudent's home, etc.)

Misunderstandings
or
What is not a contraindication for vaccination?

- Current mild acute illness with or without fever
- Recovery from recent illness
- Current antibiotic therapy
- Recent contact with infective diseases
- Breast-feeding

- Mild or moderate local reactions to a previous vaccine
- Mild or moderate fever after previous vaccination
- Allergy to antibiotics (penicillin or others.)
- Current immunotherapy with extracted allergens

Prevention of infectious diseases (Prophylaxis)

Modes

- Chemoprophylaxis: using antimicrobial drugs
- Immunoprophylaxis:
  - Active: vaccination
  - Pasive: immunoglobulins, monoclonal Ab

individually or combined

Timeing

- Pre-expoure
- Post-expoure
  - including perinatal period

Pre-exposure prophylaxis (examples)

Vaccination

- Mandatory vacccines
- Travel to risk areas: yellow fever, hepatitis A

Immunoglobulins

- Epidemic of RSV infections (bronchiolitis):

  monoclonal anti-RSV Ab for children with cystic fibrosis

Chemoprophylaxis

- Travel to malaria areas: Chloroquin

Combinations

- Non-vaccinated high risk persons during flu epidemics:

  Oseltamivir (antiviral drug) + vaccination

Postexposure prophylaxis, examples

Meningococcal diseae

- To close contact persons : Rifampin /2 days

Tetanus (lockjaw): contaminated wound

- Unvaccinated, incomplet or unknown vaccine status:
  - HTIG (human tetanus IgG) + vaccination (AnaTe)
- Fully vaccinated ≥5 years ago :
  - only booster AnaTe
- Fully vaccinated < 5 years ago:
  - nothing