



# Dermatology Vaccines and More 2016

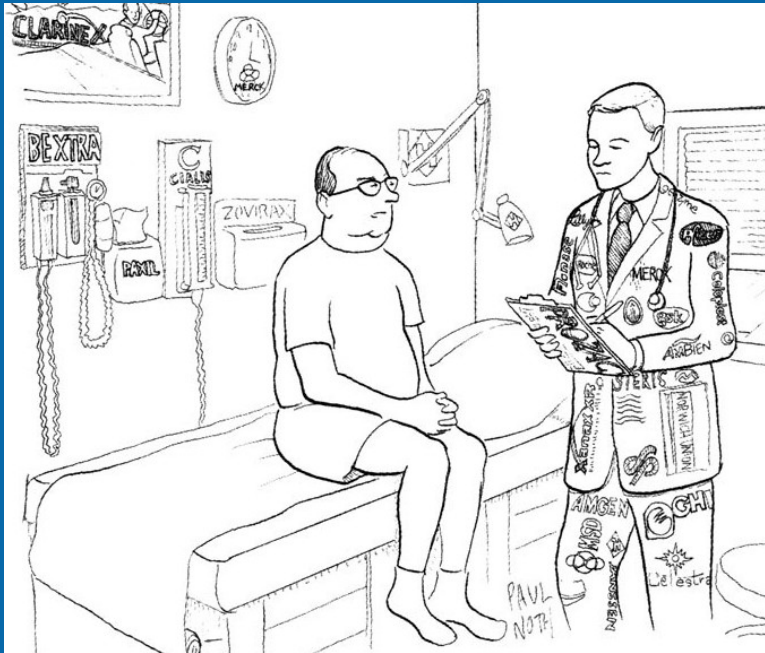
## Dermatologie Vakcíny a Více 2016

5. Brněnský Dermatologický  
Den Antonina Trýba  
Brno, CZ



Kenneth J Tomecki, MD  
Cleveland Clinic  
Cleveland, Ohio USA

# 5. Brněnský Dermatologický Den Antonina Trýba



*Dermatology Vaccines and More 2016*

Kenneth J. Tomecki MD

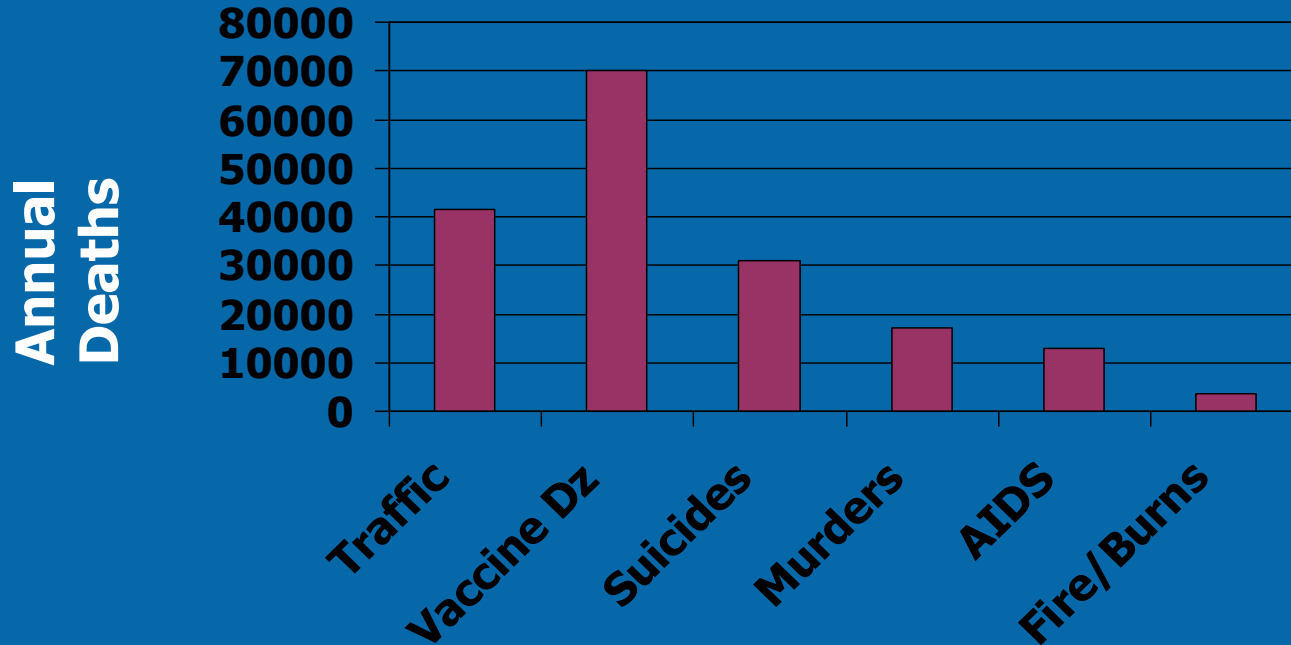
Re: Conflicts.....  
nada

# Vaccines 2016: A Medical Seatbelt

- Key aspect of medical care  
*extremely* cost effective
- Primarily Infectious Disease, eg smallpox
- Vaccine preventable diseases
- W/ vaccine neglect 50k+ deaths/ yr



# The Toll of Vaccine Neglect



The Toll of Vaccine Neglect Consumer Reports November 2001

Source: CDC incl. Death from influenza, pneumococcal dz, hepatitis, etc. Data ~ 2004

# Vaccine Rx 2016: Viruses

- Measles/mumps/rubella (MMR)
- Polio (IPV, OPV)
- Hepatitis A, inactivated (Havrix)
- Hepatitis B (plasma) combo, A and B (Twinrix)
- Influenza
- Rotavirus
- Rabies



# Vaccine Rx 2016: Viruses

- Japanese encephalitis
- Yellow fever
- Smallpox (Dryvax)
- Monkeypox
- Varicella (Varivax)
- Herpes zoster (Zostavax)
- Human papillomavirus, HPV (Gardasil, Cervarix)



# Vaccine Rx 2016: Bacteria

- Children and adults
  - diphtheria/pertussis/tetanus (DPT)
  - pneumococcal pneumonia (pneumococcus)
  - *H influenza* (hib) pneumonia
- Adolescents and adults
  - meningococemia (meningococcus)





# Vaccine Rx 2016: Bacteria

- Adults, but not routinely
  - Anthrax
- Adults, but uncommonly
  - Lyme disease, vaccine 1998, then w/drawn
  - Cholera, 4 vaccines (65-90% effective)
  - Typhoid, 2 vaccines,

but not routinely recommended



Vaccine Rx 2016: Fungi  
.....nada

Vaccine Rx 2016: Protozoa  
....nada

Vaccine Rx 2016: Parasites  
....nada

Vaccine Rx 2016: Cancer  
....promising

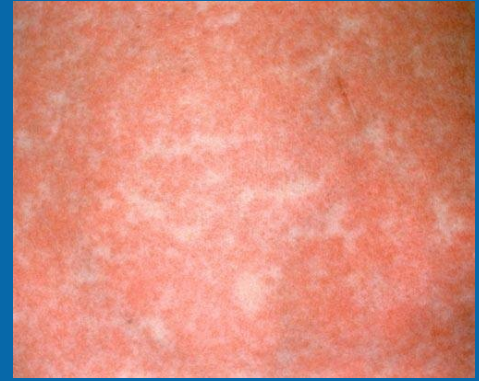


# Main Derm Vaccines 2016

- Measles / Mumps / Rubella (MMR)
- Varicella vaccine (Varivax, Proquad)
- Herpes Zoster/shingles vaccine (Zostavax)
- HPV vaccines: Cervarix; Gardasil (4/9)  
and.....hepatitis B, leprosy, BCG



# Measles / Mumps / Rubella (MMR) +Varicella 2005 (Proquad)



- Who / when?

Infants 12months+ (12-15 months); 2<sup>nd</sup> dose 4-6 years

Susceptible adults w/o measles immunity

- Advantages: obvious

# Varicella-Zoster (Varivax, Proquad\*)

- Live, attenuated VZV (Oka strain) FDA 1995
- Prevents varicella ↓ severity ↓ PHN  
↓ Incidence ↓ Morbidity/Mortality
- Varicella ↓ 90% Deaths ↓ 70%  
Immunity now 30 yrs  
? Protective duration



\*Combo vaccine w/MMR - MMRV

# Varicella-Zoster (Varivax, Proquad)

- Rx: 12 months - 12 yrs      2 doses (.5ml) SubQ  
    1st Rx @ 12-15 months, 2nd Rx @ 4-6 yrs
- Good safety and efficacy  
    97% @ 1st yr, 86% @ 2nd yr  
    81-86% @ 2-8 yrs  
    NB: 112 deaths btw 2002-2007

# Herpes Zoster -- ? Best Rx

Valacyclovir 1g 3x/day for 7 days

(vs famciclovir or acyclovir),  
plus gabapentin or pregabalin...

↓ PHN by 77%



# Zoster (shingles) Vaccine (Zostavax)

## Live attenuated VZV (Oka strain)

- Prevention of zoster and PHN
- Rx healthy adults age 50
- Rx: single, subQ dose (.65ml)
  - higher dose version of VZV vaccine (14x)
  - ↓ zoster by 50%; ↓ PHN by 65%
- ↓ efficacy @ 5 years

FDA approved June 2006



# Zoster Vaccine (Zostavax)

- Safe and effective
- Barriers
  - Shortage
  - \$\$/coverage
  - +/- MD endorsement

.....is it worth it?
- ? Protective duration      ? Need for booster



Ann Intern Med 2006;145:317  
Ann Intern Med 2006;145:387

# Herpes Zoster – A New Vaccine

## Inactivated Adjuvant Vaccine for Zoster

### VZV glycoprotein E and ASO1 adjuvant

- *HZ/su* (recomb inactivated vaccine) GSK
- Phase III: 15k+ pts >50 y/o, 18 countries
- Rx: 2 doses at 2 months
- 97% efficacy @ 3 yrs
  - ↑ w/adults age 70+

ZOE-50 Study Group  
N Engl J Med 2015;372:2087

# HPV Vaccines

- 2vHPV (Cervarix) [2], w/ASO4 adjuvant  
x-protective HPV 31, 33, 45
  - 4vHPV (Gardasil) [1,2]
  - 9vHPV (Gardasil) [1,2, etc]
- all recombinant L1 capsid    all FDA approved
- [1] HPV 6 and 11: 90% venereal warts (condyloma)
  - [2] HPV 16 and 18: 70% cervical cancer



Drugs 2010;70:1079  
JAMA 2011;205:1424

More Recently.....

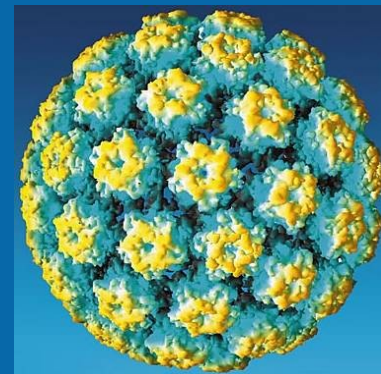
## **FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV**

- HPV 6, 11, 16, 18
- HPV 31, 33, 45, 52, 58 VLPs
- Women: 9-26; men: 9-15
- 3 doses

FDA Dec 10, 2014  
CDCP March 27, 2015 / 64(11);300-304  
N Engl J Med 2015;372:711-723

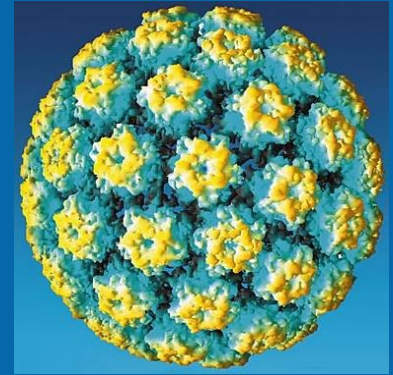
# HPV Vaccines

- Rx men and women, ages 9-26
  - 3 doses, w/in 6 months
  - 2 doses @ 6 months (15 yrs or younger)
  - Cervarix - men only
- Rx....xx pregnancy; yes for MSM



Ref: MMWR 2015 March 27;64(11):300

# HPV Vaccines



- Vaccines 95% effective -- warts and neoplasia
- Gender-neutral approach to vaccination, but.....
  - +/- acceptance, +/- promotion
  - 3 doses: 42% girls, 28% boys (CDC 2015)
  - 1 dose: 63% girls, 50% boys

US Goal: 80% by 2020

Ref: MMWR 2015 March 27;64(11):300

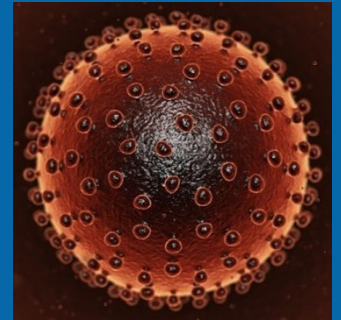
# Hepatitis B Vaccine (Recombivax HB, Engerix-B) Combo HAV and HBV (Twinrix)

## Who/when?

Pre-exposure prophylaxis, high-risk individuals;  
hemodialysis pts (ESRD); frequent transfusions;  
pts w/ diabetes; occupational exposure (medical)

# Hepatitis B Vaccine (Recombivax HB, Engerix-B) Combo HAV and HBV (Twinrix)

- Hepatitis A: 2 doses, 6-18 months apart
- Hepatitis B: 3 doses, over 6 months  
Rx: 3 doses -- 0, 1, 6 months
- Protective response: 40-90%
- Duration 20 yrs





# Leprosy: Talwar's Vaccine (Immuvac)

- Who/when?

  - Close contact, leprosy pts

  - Folks in endemic areas

- Advantages: specific/non-sp immunomodulator

  - ↑ bacterial clearance

  - converts lepromin positive → negative

? Duration: 5-7 yrs



# BCG (Bacillus Calmette-Guerin)

- Who / when?
  - Partially effective in kids: unreliable in adults
  - Rx kids and adults at risk
  - Rx those w/ occupational risk
  - Rx @ birth: ↓ meningitis ↓ miliary TB



- Advantages: tuberculin conversion  
ImmunoRx for *in situ* bladder carcinoma

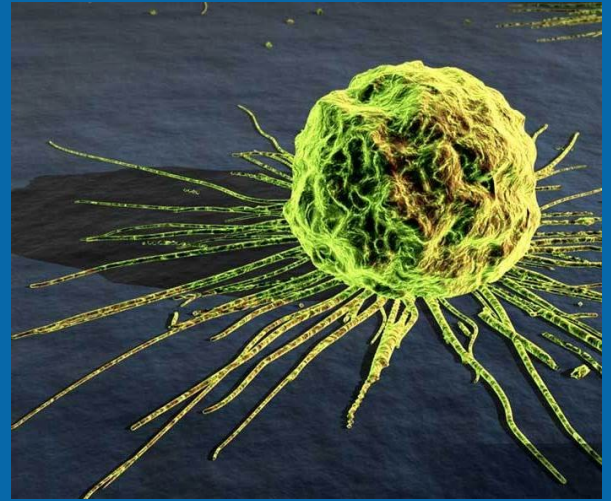
# BCG (Bacillus Calmette-Guerin)

- BCG in the USA
  - very selective use
  - ?health care workers
  - ?children (neg TB test), w/ continuous exposure
- ?Leprosy vaccine



# Cancer Vaccines

- Sipuleucel-T (provenge)
  - Rx metastatic prostate cancer
- GP-100 Peptide Vaccine / IL2
  - Rx metastatic melanoma
- Talimogene Laherparepvec (T-Vec)
  - Rx metastatic melanoma



# GP-100 Peptide Vaccine and IL-2



- 10 yr+ study      pts w/metastatic melanoma
  - Rx: vaccine and IL-2 vs IL-2 alone
    - overall response 16% w/vaccine/IL-2, vs 6% w/IL-2
    - progression-free survival 2.2 months, vs 1.5 months w/ IL-2
    - overall survival 17.8 months, vs 11.1 months w/IL-2
- promising, but.....

risk of arrhythmia w/vaccine/IL-2: 15%

N Engl J Med 2011;364:22

# Melanoma: HSV-1 ImmunoRx

## Talimogene Laherparepvec, aka T-Vec (Imlygic, Amgen)

Intralesional Rx, first oncolytic virus, FDA approved

Attenuated genetically modified HSV-1, ↑ host response via GM-CSF

- Phase 3 Optim trial, 436 pts w/metastatic non-resectable melanoma
- Durable response rate: 16%, vs 2% w/GM-CSF (\*IIIB or IIIC)
- Overall response rate: 26%, vs 5%+ w/GM-CSF
- Median survival: 23 months, vs 18 months+ w/GM-CSF



+/- promising, but.....

J Clin Oncol May 26, 2015, 3377; Sept 1, 2015, 2812

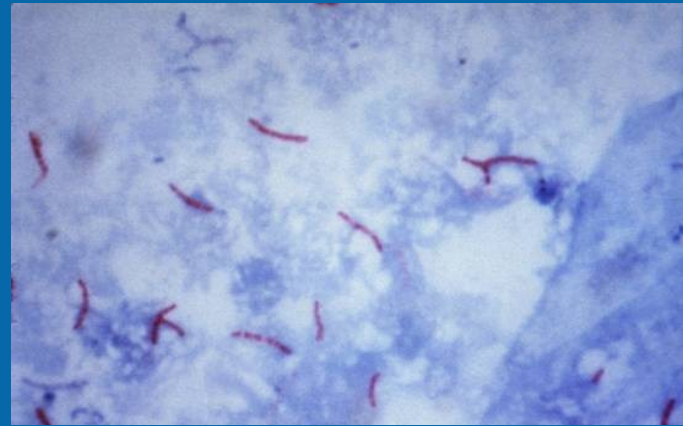
# ? Future Vaccines

- Tuberculosis
  - ?re-engineered BCG ?prime boost
  - ?molecular vaccine (several protein antigens)
- Malaria, via RTS, S
- HIV/AIDS
  - Sarnoff-Pasteur ‘prime boost’



# BCG / TB Vaccine

- BCG: ↓ TB meningitis and miliary TB
- Main concern: pulmonary TB  
    BCG: no effect
- Now, tuberculosis\* and HIV.....  
    \*latent/healed; 2 billion affected



1.3 million deaths/yr; 9-10 million new cases/yr



# Tuberculosis Vaccine

15 vaccines 'in the works' and 20+ others

Most live attenuated Mycobacteria  
or subunit vaccine proteins, w/ viral vectors

- pox viruses (MVA, fowl pox)
  - adenoviruses (AD5; Ad35)
  - vesicular stomatitis virus (VSV)
- all used as boosters

# Tuberculosis Vaccine

- NB: old *M vaccae* vaccine for pts w/latent TB and HIV  
5 intradermal doses (1 yr) HIV pts w/BCG scar
- NIH study, 2k pts Dar es Salaam  
39% efficacy vs TB

# Malaria Vaccine

RTS, S/ASO1 (RTS, S)

– Recombinant sporozoite protein + hep B surface antigen

- Phase III: 16k kids, 10 centers, 7 countries
  - 2 groups: 6-12 wks and 5-17 months
  - Rx: 4 doses q monthly x 3, then 18 months
- RTS: 27% efficacy in infants (18% w/ 3 doses)
- RTS: 39% efficacy w/ children
  
- Adv reaction: occas febrile seizures

# And Now.....Mosquirix

- 1<sup>st</sup> ever malaria vaccine
  - after 30+ years and \$565 million
- ?magic bullet...probably not, but.....
- 225 million new cases/yr
- 500k deaths/yr



# Malaria Vaccine

Definitive vaccine: more antigens (x sporozoite)

eg liver stage antigens (LSA 1 and 3),

blood (merozoite) stage antigens\* (MSP 1 and 7),

even gametocytes (Pfs25)

\*RH5 vaccine, ?complement

# Additional Needs...

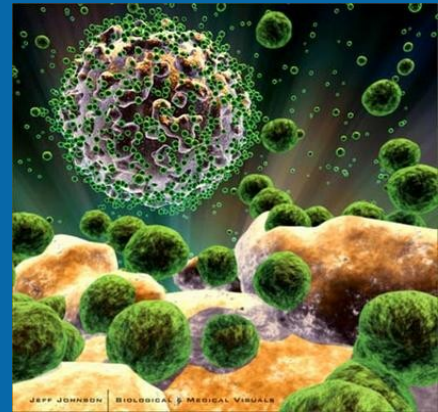
- Protozoal vaccines
  - eg Leishmaniasis, trypanosomiasis
- Metazoal vaccines
  - eg schistosomiasis, hookworms
- Parasitic vaccines
  - ? plasmid-based DNA vaccines

# HIV/AIDS Vaccine

Many disappointments

- Envelope protein-based vaccine
- ‘prime boost’ approach
- STEP trial (Merck)

Likely solution...T cell-based or antibody-based vaccine



# HIV/AIDS Vaccine

- \*Sanofi-Pasteur vaccine

Heterologous prime boost Rx

Recombinant canarypox vector vaccine (ALVA C-HIV)

w/ booster recombinant glycoprotein 120 (AIDSVAX B/E)

- RV144 trial in Thailand, 16k pts

31% efficacy, but *no effect on viral load*



# HIV/AIDS Vaccine

- Many other phase I and II trials
  - Prime boost approach,
    - w/ neutralizing anti-HIV monoclonal antibodies (PG9, PG18; VRCO)
  - HVTN study, w/ multigene, multiclade DNA
    - prime recombinant adenovirus 5 (DNA/rAd5)
- 2 million+ deaths/yr
- 2.6 million new cases/yr

# Vaccines: Current Issues / Hurdles

- Need for more combo vaccines
  - Hexavalent vaccine (diphtheria; tetanus; pertussis; H flu type B; polio; hep B)
  - Live attenuated MMR-varicella
    - ↑ febrile convulsions (2x)
- ?transdermal delivery

# Vaccines: Current Issues / Hurdles

Need for more/better adjuvants

- Toll-like receptors (TLRs)
- Nod-like receptors
- RIG-I-like receptors
- C-type lectin receptors
- Lasers, esp w/if shortages  
eg ablative fraction laser (AFL)

# Current Vaccine Adjuvants

5 licensed adjuvants..

- MF59 (Novartis)
- AS03 and AS04 (GSK)
- Liposomes (Crucell)
- AF03 (Sanofi-Pasteur)

# Vaccines: Non-scientific Issues / Hurdles

- Benefit vs fear / hesitation
- Discomfort i.e. needle sticks
- Inconvenience; cost
- ? Side effects
- Myths
- Anti-vaccination movement
- ? Need for vaccination
- ? Dangers of vaccination

# Vaccines: 'Not Just for Kids'

- Vaccines - safe and effective  
Usually only minor side effects
- True contraindications are rare  
i.e. hypersensitivity reactions, neurologic complications
- 50k+ deaths each year (USA)  
Most flu-related, 95% adults 60+



# Vaccination in General.....yes

- Avoid w/ true contraindications
- Postpone w/ moderate - severe febrile illness
- Ok to proceed
  - Current or recent mild illness, with or w/o fever, including diarrhea
  - Current or recent antibiotic Rx, *except* oral typhoid (Ty21a) vaccine
  - Previous mild/moderate rxn after vaccination
  - Personal h/o allergies
  - FH/o adv rxns to immunizations



# Vaccine Recommendations CDC, *adults 50+*

- Influenza
- Pneumococcal
- Td/dap\*
- MMR\*\*
- Zoster
- Hepatitis A
- Hepatitis B
- Meningitis

\* tetanus/diphtheria/pertussis

\*\* measles/mumps/rubella



# Influenza Vaccine

- Rx: age 50+, annually (3 strains)
- not nasal spray
  
- 33% adults (1989), 70% (2003)  
40% young adults at risk

# Pneumococcal Vaccine

- Rx: age 65+; 50+, if risk factors  
heart/lung disease, diabetes,  
lymphoma, leukemia, asthma,  
healthy adults in health care settings
- 15% adults (1989), 64% (2003)  
18% young adults at risk

# MMR Vaccine

- Rx: adults age 50+, if unsure about status  
(most exposed or vaccinated)  
? check serology, but....
- ↑ efficacy *before* pregnancy

# Td/dap\* Vaccine

- Rx: adults age 50-64 (booster)
- Td booster, age 65+
- ↑ efficacy *during* pregnancy

\* Tetanus / diphtheria / pertussis

# Tetanus/Diphtheria Immunity

## Tetanus

- Overall 30.3% susceptible
- >70 years 72.2% susceptible

## Diphtheria

- Overall 37.6% susceptible
- 50-59 years 52.8% susceptible

47% adults w/protective Abs; 91% children

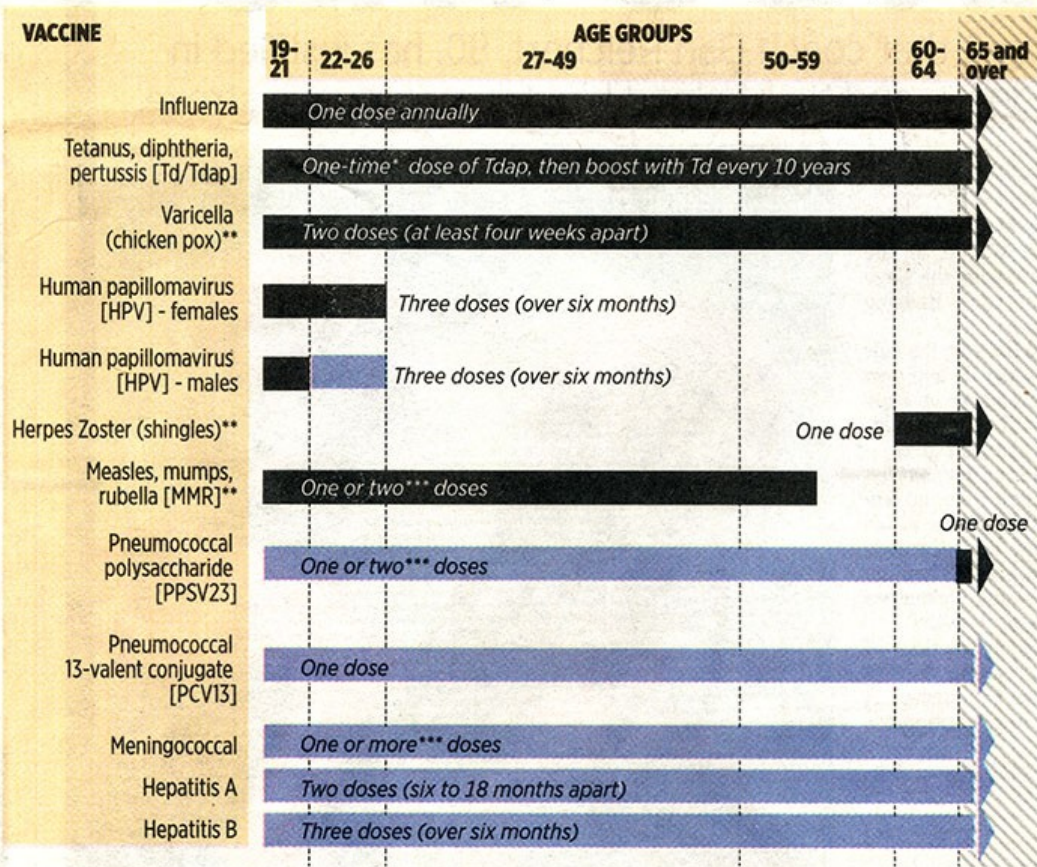
# Meningitis Vaccine

- Rx: adults age 50+, if never vaccinated or if at risk
- For adults < age 55 w/o vaccination:  
    conjugate vaccine (lifelong immunity)
- For adults > age 55: polysaccharide vaccine (3-5 yrs immunity)

CDC: Rx adults, ages 16-23, 3 doses serogroup B (MenB)

# Vaccines for Grown-Ups

■ Recommended ■ Recommended if risk factor (medical, occupational, lifestyle) is present.



\*Pregnant women need Tdap during each pregnancy.

\*\*Not recommended for pregnant women or anyone with immunocompromising conditions, including those with severe immunosuppression from HIV.

\*\*\*Need for an additional dose depends on a combination of age, risk factors, and prior immunizations.

# Routine Vaccines for Travel

## Inactivated

- Hepatitis A\*
- Tdap
- Poliomyelitis
- Influenza
- Pneumococcal

## Live-attenuated

- MMR
- Varicella

\* OK even the *day before leaving* on the trip

# Travel Specific Vaccines

## Inactivated

- Meningococcal \*
- Typhoid (Vi antigen)
- Hepatitis A †
- Hepatitis B †
- Japanese encephalitis
- Rabies

## Live-attenuated

- Yellow fever
- Typhoid (Ty21a oral)

† TwinRix combined HepA and HepB vaccine

\* New conjugate meningococcal vaccine



*"That's all Folks!"*





“Další injekce proti chřipce, Jozef.”

**Děkuji**



