8th National Seminar on Travel Medicine

19 November 2009

Vaccination of the immunocompromised travellers

15.15 - 15.45

Vaccination of the immunocompromised travellers

Prof F. Van Gompel, ITG Antwerpen

ST CONFERENCE ON
MMUNO-
COMPROMISED
RAVELLER

March 26-27, 2009
Maastricht
The Netherlands

Adapted & updated version 19-11-2009

Vaccination of immunocompromised patients with inflammatory diseases

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Vaccinations in patients with immune-mediated inflammatory diseases

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Submitted J Autoimmunity

Content

1. Inflammatory diseases & Immunomodulatory drugs
2. Efficacy and safety of a vaccine
3. Travel medicine
4. Which vaccines for adults ?
5. Which vaccines are recommended in immunocompromised patients with immune mediated inflammatory diseases
6. Timing of vaccination
7. Live vaccines : prototype Yellow fever vaccine; Zoster
8. Measurement immune status & Serologic control

Inflammatory diseases

- **Rheumatic diseases** : Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Psoriatic Arthritis (PA), Ankylosing Spondylitis (AS) and other spondylarthropathies, Juvenile Idiopathic Arthritis (JIA) , (connective tissue diseases, vasculitides)
- **Inflammatory Bowel Diseases** : Ulcerative Colitis, Crohn's disease
- **Skin** : Psoriasis

- Many other « inflammatory / autoimmune diseases » exist: e.g. glomerulonephritis, multipele sclerose, idiopathic thrombopenic purpura, myasthenia gravis, M. Behçet, sarcoïdosis, auto-immune hepatitis, ….

Inflammatory disease - a cause in itself for immunodepression possibly influencing efficacy / safety of vaccines ?

The physiopathology for these diseases is different

- **RA & LE** **YES** (according to disease activity !?)

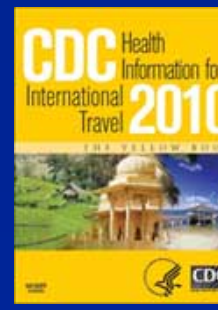
MF Doran et al. Arthritis Rheum 2002

- **IBD** "NO" (defective innate immunity ?)
- **Psoriasis** "NO"

Immunomodulatory drugs are a more important cause for immunodepression

Immunomodulatory drugs commonly used may/will influence efficacy / safety of vaccines

- Corticosteroids
  (high dose → 20 mg/day of prednisone or equivalent for ≥2 weeks)
- Methotrexate including low-dose weekly regimens *(not considered by all rheumatologists as severely immunocompromising)*
- Leflunomide *(considered by most rheumatologists as immunocompromising*)
- Alkylating agents (e.g., cyclophosphamide)
- Antimetabolites (e.g., azathioprine, 6-mercaptopurine)
- Transplant-related immunosuppressive drugs (e.g., cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil)
- Mitoxantrone (used in multiple sclerosis).



BIOLOGICALS

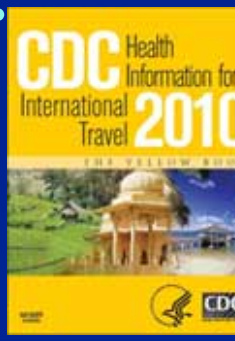
- Anti Tumor Necrosis Factor α agents
  (infliximab, adalimumab, etanercept, certolizumab, golimumab)
- Others: rituximab (anti CD20), anakinra (human interleukine-1-receptorantagonist), abatacept (anti T cell costimulation (CTLA4)), tocilizumab (anti IL6 receptor), efalizumab …

Immunomodulatory drugs commonly used may influence Efficacy / Safety of vaccines

Mode of action of immunosuppressive drugs in solid-organ transplant recipients

Immunosuppressive agents	Clinical use	Mode of action
Corticosteroids	Basic immunosuppression Pulse therapy for acute rejection	Modification of antigen presentation and processing Inhibition of IL-1, IL-2, TNF-α, IFN-γ, and NFκB
Azathioprine	Basic immunosuppression	Purine nucleotide analogue Inhibition of rapidly proliferating cells
Calcineurin inhibitors (ciclosporin A, tacrolimus [FK 506])	Basic immunosuppression	Calcineurin inhibition Inhibition of the transcription factor nuclear factor of activated T cells (NFAT) Inhibition of IL-2-dependent growth and differentiation of activated lymphocytes Direct or indirect inhibition of B-cell synthesis
Sirolimus	Basic immunosuppression	Inhibition of DNA and protein synthesis Inhibition of several cytokines Direct and indirect inhibition of B-cell synthesis
Mycophenolate mofetil	Basic immunosuppression	Inhibition of inosine monophosphate dehydrogenase, an enzyme of the de-novo purine pathway Blockade of inosine monophosphatase Inhibition of T cells and B cells

NB: Not immunocompromising :



- Paracetamol (?) & NSAID
- Sulphasalazine & (hydroxy)chloroquine
- Corticosteroids
  - Short- or long-term daily or alternate-day therapy with <20 mg of prednisone or equivalent
  - Long-term, alternate-day treatment with short-acting preparations
  - Maintenance physiologic doses (replacement therapy)
  - Steroid inhalers
  - Topical steroids (skin, ears, or eyes)
  - Intra-articular, bursal, or tendon injection of steroids
  - Budesonide enteric coated (Entocort ®, etc)…?

NB: Not immunocompromising ? :

- Glatiramer acetate (MS) **not**
- Hydrea **very probably not**
- Monoclonal antibodies against VEGF (vascular endothelial growth factor), EGFR (epidermal growth factor), growth factor HER-2 (Herceptin ®) **very probably not**
- Tyrosine kinase inhibitor (Glivec ® ..) **probably yes**
- ……. **probably not** / **yes**

Interferons (a, b and g) and ribavirin

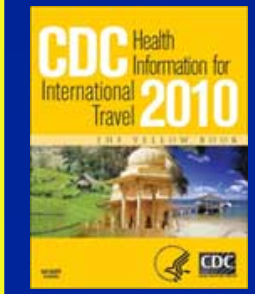
- Risk for neutropenia, but no clinically apparent increase in opportunistic infections.
- No information is available on
  - possible decreased vaccine efficacy (physiopathologically plausible)
  - increased adverse events with live viral antigens (physiopathologically not plausible; on the contrary it will inhibit intracellular viral multiplication)

  but definitive data are lacking.
- In general not considered to compromise immunity
- No formal contraindication for YF vaccination
- Quid Pegylated-interferon ? probably immunodepressive ?

Severely immunocompromised (non-HIV) persons include those who have

- Congenital immunodeficiency
- (active) Leukemia or lymphoma
- Generalized malignancy
- Cancer chemotherapeutic agents (excluding tamoxifen and other (anti-)hormonal medications).
- Radiation therapy, current or recent (*total body irradiation; megavoltage wide field radiotherapy; "mantle field irradiation"*)
- Solid organ transplantion or bone marrow transplantion or stem cell transplantation (HSCT) within 2 years;

  persons whose transplants occurred >2 years ago but who are still taking immunosuppressive drugs.
- Graft-versus-host disease
- Aplastic anemia



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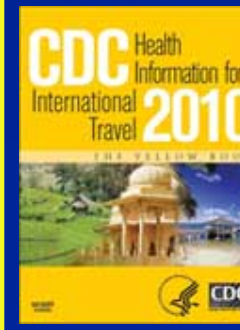
Other Conditions Associated with Immune Deficits

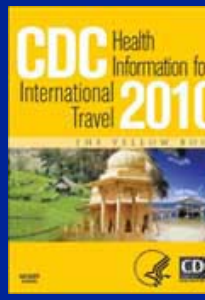
- HIV Infection
  - Asymptomatic HIV-infected persons with CD4 cell counts of 200–500/mm3 are considered to have limited immune deficits
  - HIV-infected persons with CD4 cell counts <200/mm3, history of an AIDS-defining illness, or clinical manifestations of symptomatic HIV are considered to have severe immunosuppression

- Thymectomy and thymoma



Chronic Conditions Associated with **Limited** Immune Deficits include

- Asplenia
- Chronic renal disease (uremic state in end stage renal disease & haemodialysis patients)
- Chronic liver disease (including chronic hepatitis C)
- Diabetes mellitus
- Complement deficiencies
- *Various forms of localized radiotherapy*
- *Tamoxifen and other (anti-)hormonal medications).*
- *Severe malnutrition*
- *Diabetes mellitus*
- *Immmunoscenescentie*
- *(chronic lung & heart failure)*
- *(IV drug users)*



Infections in corticosteroid treated patients (meta-analysis)

Daily dose pred	RR (incidence per 100 pt)	Incidence per 1000 pt.21 days
< 20 mg	1.3 (1.0-1.6)	5.8 (NS)
20-40 mg	2.1 (1.3-3.6)	22.6 (p 0.004)
> 40 mg	2.1* (1.6-2.9)	150.7 (p 0.001)

*shorter duration of high dose (median 12 days versus 28 days)

Stuck AE, et al. Rev Infect Dis 1989; 11: 954-963.

Infections in corticosteroid treated patients (meta-analysis)

Cumulative dose pred	RR (incidence per 100 pt)	Incidence per 1000 pt.21 days
< 500 mg	0.9 (0.1-6.6)	12.2 (NS)
500-999 mg	2.0 (1.0-3.9)	49.1 (p 0.06)
> 1000 mg	2.6 (1.5-4.6)	83.9 (p 0.001)

Stuck AE, et al. Rev Infect Dis 1989; 11: 954-963.

REVIEWS OF INFECTIOUS DISEASES • VOL. 11, NUMBER 6 • NOVEMBER-DECEMBER 1989

Risk of Infectious Complications in Patients Taking Glucocorticosteroids

Andreas E. Stuck, Christoph E. Minder, and Felix J. Frey

From the Medizinische Poliklinik and Institut für Sozial- und Präventivmedizin, University of Berne, Switzerland

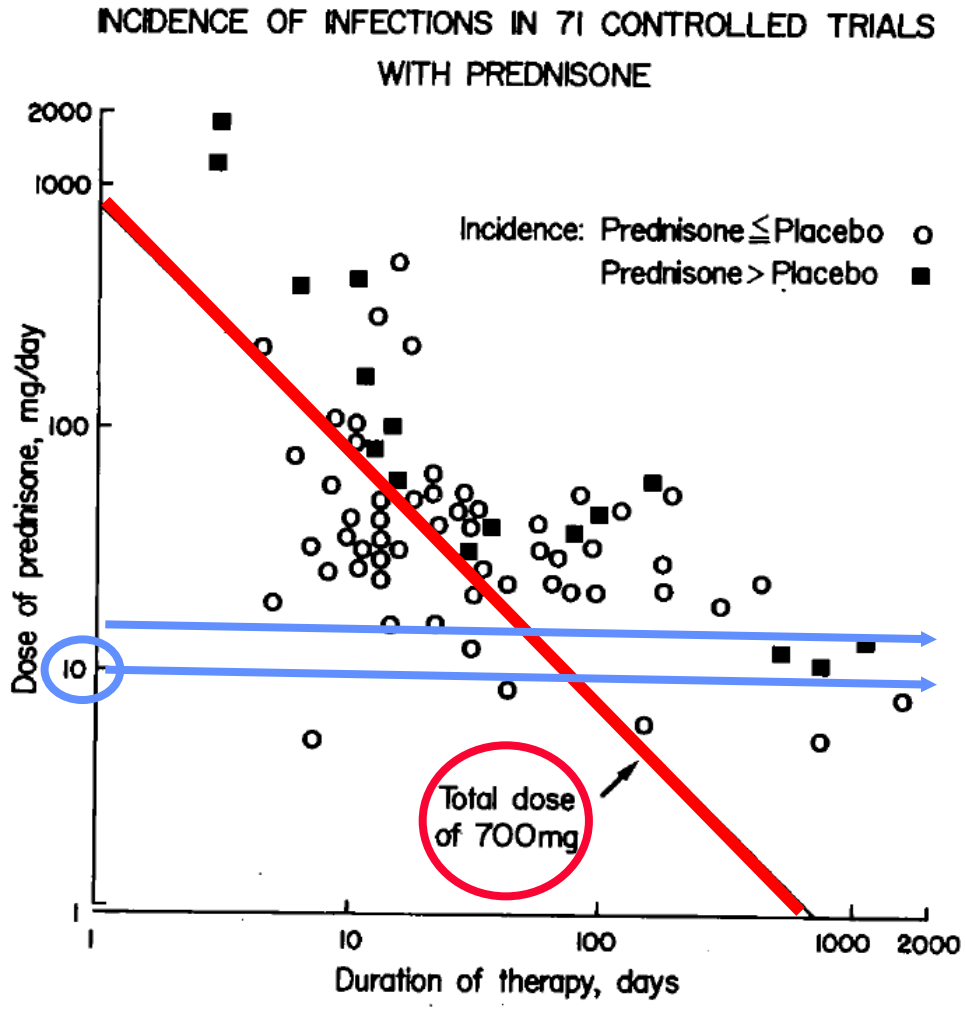


Figure 1. Double-logarithmic plot of the mean daily dose of prednisone vs. the median duration of therapy in 71 controlled trials. Each symbol represents one trial. The position of a symbol reflects the mean daily dose of prednisone (*y* axis) and the median duration of therapy prescribed (*x* axis) in a given trial. The closed squares (■) represent trials with a higher numerical incidence of infectious complications in the group of patients treated with prednisone than in the group of controls, whereas the open circles (○) represent trials without a higher incidence of infectious complications in patients given prednisone than in controls. The product of the duration of therapy times the daily dose is the cumulative dose of prednisone prescribed. The cumulative dose of 700 mg of prednisone is given by the oblique line. Note that all trials with a higher incidence of infections in patients given prednisone than in those given placebo are located above the isodose line of 700 mg, an indication that, independent of the dosage regimen, patients with a cumulative dose of <700 mg had no increased risk of infectious complications.

Corticosteroids

- Most autorities accept at this moment :
  - "low dose corticosteroids" (< 20 mg) is no contraindication (despite high cumulative dose)
- National Consensus Travel Medicine 2009
  - The contraindication level for corticosteroids remains ≥ 20mg prednisolon for ≥ two weeks.
  - Prednisolon < 10mg is no contraindication.
  - Prednisolon between 10 and 20mg requires expert advice, taking into account underlying disease and its immunosuppressive character as well as current and cumulative dose.

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Efficacy of vaccines

in the context of immunodepressed patients

Response to the vaccine may be decreased resulting in poor protection

- **Efficiency / field efficacy**
  - preferably trough well-conducted and well-controlled vaccine efficacy trials different possible end points (infection, disease, hospitalization, death) in different settings and populations
  - rarely possible or feasible in the context of immunodepressed patients…
- **Immunogenicity**

Efficacy of vaccines

in the context of immunodepressed patients

Response to the vaccine may be decreased resulting in poor protection

- **Efficiency / field efficacy**
- **Immunogenicity = immunological markers** (of the adaptive immune system) used as "correlate" and/or "surrogate" of protection (against infection and / or disease)

  - MOST OFTEN **humoral** = demonstration of B cell–generated antibodies
    - quantitatively = seroconversion & geometric mean titers / peak titers
    - quality = e.g. avidity; bactericidal / opsonophagocytitic / neutralizing ab; etc
    - rapidity of decline of titers or long term persistence

  - ALSO **cellular** markers : effector T cells / memory B & T cells

Efficacy of vaccines

in the context of immunodepressed patients

Immunogenicity and Safety of Hepatitis A Vaccine in Liver and Renal Transplant Recipients JID 1999 180 2014

= "lower (PR), slower, lower (GMT), shorter"

Table 1. Anti–hepatitis A virus (anti-HAV) response following vaccination with hepatitis A vaccine in initially anti-HAV–seronegative liver transplant (LTX) patients, renal transplant (RTX) patients, and healthy controls.

Variable	LTX patients (n = 39)	RTX patients (n = 39)	Controls (n = 29)	P
No. (%) responding				
After dose 1	16/39 (41.0)	9/38 (23.7)	26/29 (89.7)	<.0001
After dose 2	37/38 (97.4)	28/39 (71.8)	27/27 (100)	<.001
GMT (95% CI)[a]				
After dose 1	101 (33–164)	17 (11–26)	169 (97–313)	—[b]
After dose 2	1306 (560–2903)	85 (48–151)	1596 (1093–2652)	—[c]

[a] GMT, geometric mean titer, in mIU/mL; CI, confidence interval.

[b] RTX vs. LTX, $P < .01$, $z = -2.8$; LTX vs. controls, $P < .05$, $z = -2.2$; RTX vs. controls, $P < .0001$, $z = -5.7$ (Mann-Whitney test).

[c] RTX vs. LTX, $P < .0001$, $z = -5.2$; LTX vs. controls, $P = .35$, $z = -0.9$; RTX vs. controls, $P < .0001$, $z = -5.8$ (Mann-Whitney test).

Vaccination in Patients with Chronic Rheumatic or Autoimmune Diseases

RA

T. Glück[1] and U. Müller-Ladner[2,3]

Clinical Infectious Diseases 2008; 46:1459–65

Only relatively **small studies** have investigated the influence of **DMARDs** on the immunogenicity of **pneumococcal and influenza vaccine** in patients with chronic rheumatic and autoimmune diseases,

and these studies **do not result in a uniform picture !!!!!!!!!**

Immunization of patients with rheumatoid arthritis with antitumor necrosis factorα therapy and methotrexate

Hans-Peter Brezinschek[a], Thomas Hofstaetter[a], Burkhard F. Leeb[b], Pia Haindl[b] and Winfried B. Graninger[a]

Current Opinion in Rheumatology 2008, 20:295–299

Table 1 Effect of drug combinations in rheumatoid patients on antibody response

Antibody response	Vaccine	DMARD	Additional TNF-Therapy	References
Decreased	Influenza vaccine	Methotrexate	Etanercept, infliximab	[8•]
	Influenza vaccine	–	Etanercept, infliximab	[8•]
	Pneumococcal vaccine	Methotrexate	–	[7••,15,16]
	Pneumococcal vaccine	Methotrexate	Adalimumab	[7••]
	Pneumococcal vaccine	Methotrexate	Etanercept, infliximab	[15]
Not decreased	Influenza vaccine	Methotrexate	–	[4–6,7••,8•,9–11]
	Influenza vaccine	Methotrexate	Adalimumab	[7••]
	Influenza vaccine	Methotrexate	Etanercept, infliximab	[6]
	Pneumococcal vaccine	Methotrexate	Infliximab	[18]
	Pneumococcal vaccine	–	Adalimumab	[7••]
	Pneumococcal vaccine	–	Etanercept, infliximab	[15,16,18]
	Hepatitis B vaccine	Methotrexate	–	[25,26]

DMARD, disease-modifying antirheumatic drug; TNF, tumor necrosis factor.

Vaccination in Patients with Chronic Rheumatic or Autoimmune Diseases

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Clinical Infectious Diseases 2008; 46:1459–65

SUMMARY

Conventional DMARDs, such as **methotrexate** or **azathioprine**, appear to have only modest impact on postvaccination titers.
In general, 20% — in some studies, up to 50% — of the patients do not develop protective antibody levels.

Among the newer, "biological" DMARDs, the **TNF antagonists** also appear to only slightly diminish antibody responses to vaccines.

In contrast, the preliminary data available thus far for **rituximab** (anti CD20), and **abatacept** (anti T cell costimulation (CTLA4)), show that these agents may have the potential to blunt immune responses, and more studies of these agents are urgently needed.

Immunization of patients with rheumatoid arthritis with antitumor necrosis factorα therapy and methotrexate

Hans-Peter Brezinschek[a], Thomas Hofstaetter[a], Burkhard F. Leeb[b], Pia Haindl[b] and Winfried B. Graninger[a]

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SUMMARY

Regarding **influenza** vaccination,

- MTX monotherapy is not associated with a decreased response,
- the use of etanercept and infliximab in combination with MTX may cause lower titers and lower response rates.

Concerning **pneumococcal** vaccination,

- MTX seems to impair responsiveness;
- the concomitant use of adalimumab and MTX is also associated with decreased response,
- the concomitant use of etanercept or infliximab and MTX seems not to have an effect on response rates.

FC02.03

A Study on the Effectiveness of Hepatitis A Vaccination in Travelers with Immunosuppressive Medication

H. ter Waarbeek[1,2], *N. Dukers-Muijrers*[1,2], *C. Hoebe*[1,2]

[1]South Limburg Public Health Service, Infectious Diseases, Geleen, Netherlands, [2]Maastricht Infection Center, University Hospital, Maastricht, Netherlands

Over the past decades the number of people with an immunodeficiency disorder traveling abroad has increased. However, immunocompromised travelers respond differently to the recommended vaccinations, which may lower the effectiviness. Measurement of antibody titers can determine whether they develop adequate protection. This paper explores the effectiveness of hepatitis A vaccination in travelers with immunosuppressants. Data from 56 immunocompromised travelers from our travel clinic were analyzed. Sex, age, medical condition, medication, travel destination and response to hepatitis A vaccination were compared, based on a standardised questionnaire and measurement of the hepatitis A antibody titer. A total anti-HAV titer of < 20 u/L shows an insufficient protective level (non-responder).

Of these travelers 31% were female. The average age was 42 (range 9-74). In total 29% were non-responders (male 26% and female 31%). Younger travelers (< 40) showed no significant difference (p=0.67) in protective titers compared to older travelers (32% (7/22) vs 26% (9/34) non-responders). Travelers mostly presented with rheumatoid arthritis (36%), followed by inflammatory bowel diseases (21%), organ transplants (9%), psoriasis (9%), malignancies (9%) and other (16%). Corticosteroids were the most frequently drugs taken (35%), next to Methotrexate (27%), Mercaptopurine derivates e.g. Azathioprine (12%) and TNF-blockers (10%). Other drugs included Tacrolimus, Interferon, Cyclosporine and other chemotherapeutics. 43% of travelers using Methotrexate, 28% of those using Corticosteroids and 20% taking TNF-blockers did not develop a sufficient anti-HAV titer, whereas all travelers who took Mercaptopurinederivates achieved protective titers. Both travelers using Tacrolimus did not develop adequate titers.

This study shows that a large proportion of travelers taking immunosuppressive medication are not sufficiently protected after hepatitis A vaccination and therefore require special attention. They should always be offered titer measurement after vaccination. Furthermore, neither sex nor age seem to influence the immune response. However, a difference could be seen in the effectiveness of vaccination depending on the type of immunosuppressants being taken. Further research on the influence of immunosuppressive medicines on response to vaccination as well as studies evaluating the best way to vaccinate immunocompromised travelers should be done.

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did not develop a sufficient anti-HAV titer:

- **43% of travelers using Methotrexate**
- **28% of those using Corticosteroids**
- **20% taking TNF-blockers**
- **both travelers using Tacrolimus**

all travelers who took mercaptopurinederivates achieved protective titers.

Safety of vaccines

in the context of immunodepressed patients

Vaccines may cause ?

- **Hypothetical** = **Flare up** of the inflammatory disease / rejection / hiv ……
  - *(temporal association in only a very few case reports; no causal relationship demonstrated)*
  - *(substantial literature data supports the conclusion that immunisation does not increase clinical or laboratory parameters of disease activity)*
  - *1976 swine flu & GBS; measles & ITP*
  - ***VIGILANCE remains important !! Cfr HPV, H1N1 new variant (= adjuvants)***

- **Possible** = **Dissemination** of the virus of **live vaccines**
  (? enhanced virus replication? , with risk for **severe side effects, persistence of the virus, transmission to the environment) – e.g. OPV**

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TRAVEL CLINIC : How often ?

Factors Influencing Standard Pretravel Health Advice—A Study in Belgium

Journal of Travel Medicine, Volume 14, Issue 5, 2007, 288–296

Kristina Van De Winkel, MD,* Alex Van den Daele, RN,* Alfons Van Gompel, MD,* and Jef Van den Ende, MD, PhD*†

2,227 travelers
ITM pretravel clinic
Oct & Nov 2004

In the past few years, we have seen several patients with stable Crohn's disease taking cyclofosfamide or with rheumatoid arthritis treated with methotrexate or even anti-tumor necrosis factor (TNF) medication, who walked in at our pretravel practice, not expecting the unwelcome surprise of a refused yellow fever vaccination.

14 took Immunosuppressive medications for RA, SLE, IBD, Psor, post-transplant, etc

Not all needed yellow fever vaccination (did not visit YF-endemic countries, or were vaccinated against YF less than 10 years ago)

It was actually a problem in 4 – they changed their itinerary

Revista da Sociedade Brasileira de Medicina Tropical 42(1):23-27, jan-fev, 2009

Vaccination against yellow fever among patients on immunosuppressors with diagnoses of rheumatic diseases

- Retrospective study applied to rheumatological patients who were using immunosuppressors and were vaccinated 60 days before the investigation by means of a questionnaire
- 70 patients of mean age 46 years were evaluated.
  - 54 RA
  - 11 SLE
  - 5 spondyloarthropathy
  - 2 systemic sclerosis
- The therapeutic schemes included
  - MTX (42)
  - CSt (22)
  - sulfasalazine (26)
  - leflunomide (18)
  - cyclophosphamide (3)
  - immunobiological agents (9)
- Sixteen patients (22.5%) reported some minor adverse effect.
- **Among the eight patients using immunobiological agents**, only one presented a mild adverse effect.
- Among these patients using immunosuppressors, adverse reactions were no more frequent than among immunocompetent individuals.

“This is the first study on this topic”.

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Vaccines for adults

Immunocompromised patients with inflammatory disease may be at higher risk ?

Routine vaccinations:

Tetanus	No
Diphtheria	No
Pertussis	No
Polyomyelitis	No
Measles	**Yes**

In selected groups:

Invasive Pneumococcal Disease	**Yes**
Influenza	**Yes**
Hepatitis B	**Yes**

Human Papilloma virus	**Yes**
Varicella /Zoster	**Yes**

e.g. CDC; (CATMAT) The Immunocompromised Traveler. 04/2007

Vaccines for adults

Immunocompromised patients with inflammatory disease may be at higher ris

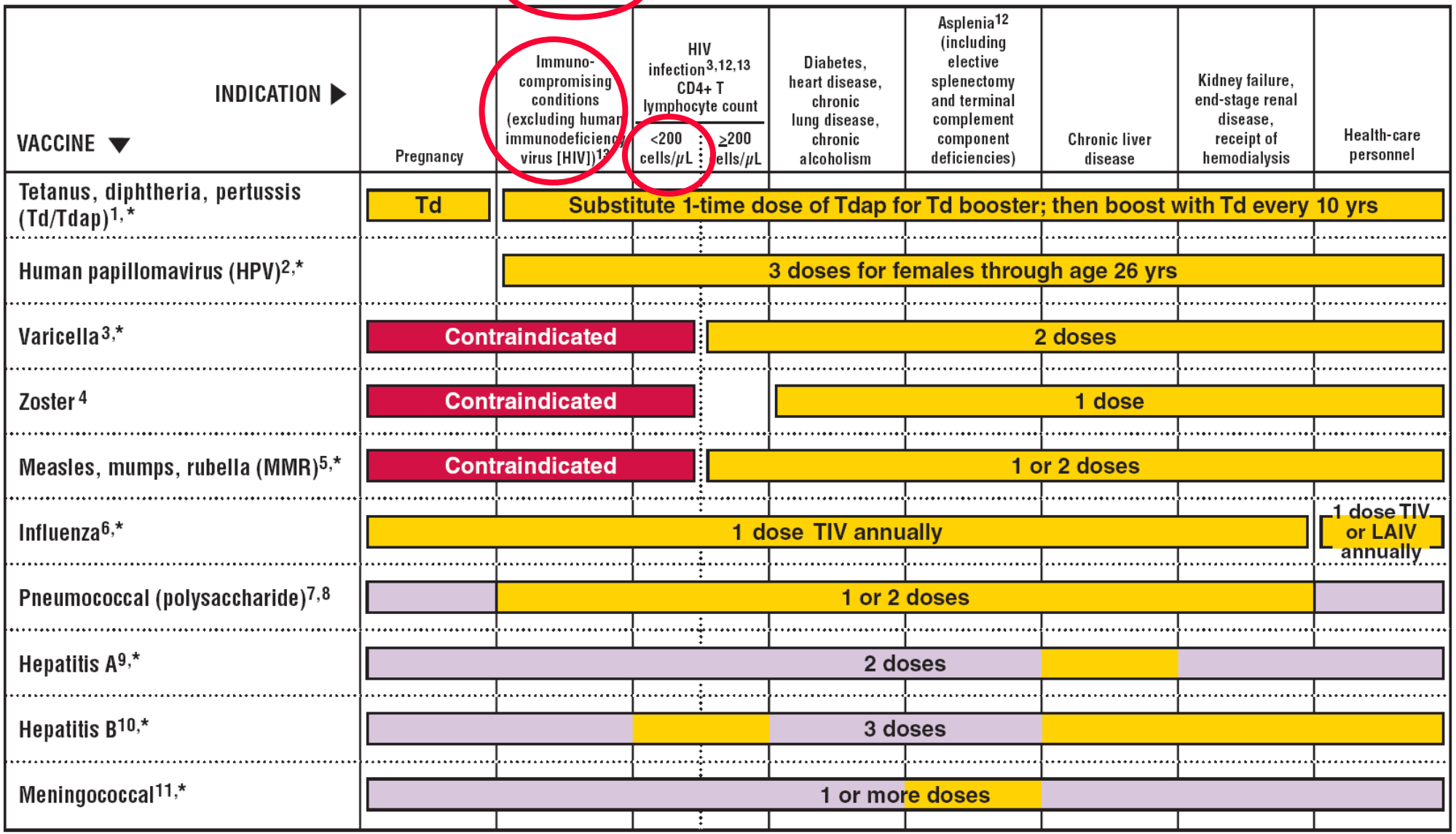
Travel related vaccine:

Hepatitis A	No
Typhoid fever	No ?
Yellow fever	No ?
Meningococcal meningitis	No ?
Japanese encephalitis	No
Tick born encephalitis	No ?
Rabies	No
(TBC/BCG)	***Yes***
Cholera	*No ?*

e.g. CDC; (CATMAT) The Immunocompromised Traveler. 04/2007

http://www.cdc.gov/mmwr/PDF/wk/mm5753-Immunization.pdf

FIGURE 2. Vaccines that might be indicated for adults based on medical and other indications — United States, 2009



*Covered by the Vaccine Injury Compensation Program.

For all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have no evidence of prior infection)

Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)

No recommendation

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IBD

European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease

JF Rahier, S Ben-Horin, Y Chowers, C Conlon, P DeMunter, G D'Haens, E Domenech, R Eliakim, A Eser, J Frater, M Gassull, M Giladi, A Kaser, M Lémann, T Moreels, A Moschen, R Pollok, W Reinisch, M Schunter, EF Stange , H Tilg, G Van Assche, N Viget, B Vucel Walsh, G Weiss, Y Yazdanpanah, Y Zabana, SPL Travis, JF Colombel on behalf of the European Crohn's and Colitis Organisation (ECCO)

JCC (Journal of Crohn's disease and Colitis) 2009 (in press)

PSORIASIS

From the Medical Board of the National Psoriasis Foundation: Monitoring and vaccinations in patients treated with biologics for psoriasis

M Lebwohl et al.,
J Am Acad Dermatol 2008;58:94-10

LUPUS

Immunizing patients with systemic lupus erythematosus: a review of effectiveness and safety

SG O'Neill* and DA Isenberg
Centre for Rheumatology, University College London, London, UK

Lupus (2006) 15, 778–783
www.lupus-journal.com

RA

British Society for Rheumatology 2002,
http://rheumatology.org.uk/guidelines/guidelines_other/vaccinations/view

American College Rheumatology 2008 oral presentation (Monday 27/10/2008)

European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease

J.F. Rahier*, S. Ben-Horin, Y. Chowers, C. Conlon, P. De Munter, G. D'Haens, E. Domènech, R. Eliakim, A. Eser, J. Frater, M. Gassull, M. Giladi, A. Kaser, M. Lémann, T. Moreels, A. Moschen, R. Pollok, W. Reinisch, M. Schunter, E.F. Stange, H. Tilg, G. Van Assche, N. Viget, B. Vucelic, A. Walsh, G. Weiss, Y. Yazdanpanah, Y. Zabana, S.P.L. Travis, J.F. Colombel
on behalf of the European Crohn's and Colitis Organisation (ECCO)

IBD

Journal of Crohn's and Colitis (200

This paper is the product of work by gastroenterologists and infectious disease experts.

It provides guidance on the prevention, detection and management of opportunistic infections in patients with IBD.

After a section on definitions and risk factors for developing opportunistic infection, there are five sections on different infectious agents,
followed by a **section on information and guidance for patients with IBD travelling frequently or to less economically developed countries.**

In the final section, a systematic work up and **vaccination programme** is proposed for consideration in **patients exposed to immunomodulator therapies**.

IBD

European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease

1/As in the general population, the immunisation status of patients with inflammatory bowel disease should be checked and vaccination considered for **routinely administered vaccines: tetanus, diphtheria, poliomyelitis.**

2/ In addition, every patient with inflammatory bowel disease should be considered for the five following vaccines, ideally at diagnosis for the reasons above:

- **VZV varicella vaccine** (if there is no medical history of chickenpox, shingles, or VZV vaccination and VZV serology is negative)
- **Human papilloma virus**
- **Influenza** (trivalent inactivated vaccine) once a year
- **Pneumococcal polysaccharide vaccine** booster after 5 years
- **Hepatitis B vaccine** in all HBV seronegative patients

3/ **Vaccines** for patients on immunomodulators **traveling in developing countries or frequently traveling around the world** should be discussed with an appropriate specialist – **live vaccines** are not allowed – TB check.

Which vaccines are recommended in IC patients ?

HP Brezinschek et al., Curr Opin Rheumatol 2008 ; B Sands et al., Inflamm Bowel Dis 2004
JF Rahier et al., JCC 2009 (in press); M Lebwohl et al., J Am Acad Dermatol 2008
British Society for Rheumatology 2002,
http://rheumatology.org.uk/guidelines/guidelines_other/vaccinations/view
Superior Health Council www.health.fgov.be/CSS_HGR
CDC http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5515a1.htm

Patients with inflammatory disease

Vaccine	Impact disease in IC patients ?	Belgian Superior Health Council	CDC	Britisch Society for Rheumatol.	European Crohn & Colitis Org.	Am. Psoriasis Found.
Influenza	Increased mortality	YES	YES	YES	YES	YES
Pneumo	Increased mortality	subgroups	YES	YES	YES	
HPV	Increased morbidity				YES	
Varicella/ Zoster	Increased mortality		(YES)	YES	YES	
HBV	Increased morbidity	subgroups	Sub groups	(yes)	YES	

From the Medical Board of the National Psoriasis Foundation: Monitoring and vaccinations in patients treated with biologics for psoriasis

PSORIASIS

J Am Acad Dermatol 2008;58:94-10

Table I. Adult immunization recommendations approved by the Advisory Committee on Immunization Practices, the American College of Obstetrics and Gynecology, and the American Academy of Family Physicians[133]

Vaccine	
Tetanus, diphtheria, pertussis	Administer to all persons who lack evidence of immunity.* Booster is recommended every 10 y.
Human papillomavirus	3 Doses recommended for women and girls < age 26 y.
Measles, mumps, rubella	Recommended for individuals < age 50 y who lack evidence of immunity and for selected individuals at high risk > age 50 y.
Varicella	Vaccine recommended for individuals < age 50 y who lack evidence of immunity and for selected individuals > age 50 y. Note that this is a live vaccination that should not be administered to patients already taking biologics.
Herpes zoster	For selected individuals ≥ age 60 y. Note that this is a live vaccine that should not be administered to patients already taking biologics.
Influenza	For selected† individuals < age 50 y and for individuals ≥ age 50 y annually. Note that inactivated influenza vaccine should be used for patients already taking biologics.
Pneumococcal polysaccharide vaccination	For selected individuals < age 65 y and for all individuals ≥ age 65 y who lack evidence of immunity.
Hepatitis A	For selected individuals at high risk.
Hepatitis B	For selected individuals at high risk.
Meningococcal vaccination	For selected individuals at high risk.

*Theoretic reasons for vaccination are agreed on by members of this consensus conference, but there was variation in the vaccination practices of participating experts.

†Several, but not all, experts advocate annual influenza vaccination in patients taking biologic agents.

From the Medical Board of the National Psoriasis Foundation: Monitoring and vaccinations in patients treated with biologics for psoriasis

PSORIASIS

J Am Acad Dermatol 2008;58:94-10

Table II. Key monitoring and vaccination recommendations in product package inserts

Biologic	Monitoring recommendations	Vaccination recommendations
Adalimumab	Tuberculin skin test before therapy	Avoid live vaccines
Alefacept	$CD4^+$ T-lymphocyte counts before and every 2 wk during each 12-wk course	Live or live-attenuated vaccines not studied; response to tetanus toxoid and experimental neoantigen preserved
Efalizumab	Platelet counts every month on initiation of therapy and eventually every 3 mo	Acellular, live, and live-attenuated vaccines should not be given while on efalizumab
Etanercept		Immunize before initiating etanercept; patients may receive concurrent vaccines except for live vaccines
Infliximab	Tuberculin skin test before starting therapy; patients with signs or symptoms of liver dysfunction should be evaluated for evidence of liver injury	Immunize before initiating infliximab; avoid live vaccines

Note that monitoring recommendations in package inserts may be incomplete.

From the Medical Board of the National Psoriasis Foundation: Monitoring and vaccinations in patients treated with biologics for psoriasis

PSORIASIS

J Am Acad Dermatol 2008;58:94-10

Table III. Tests and vaccinations to consider when treating patients with biologic agents for psoriasis

Hematology CBC + Plt	Chemistry screen with LFTs	ANA	TB skin test	Vaccinations
Adalimumab	BL	BL optional	BL and annually	BL standard vaccinations*
BL and every 2-6 mo	Every 2-6 mo			Annual inactivated influenza
Alefacept	BL		BL and annually	BL standard vaccinations*
CD4+ BL and every 2 wk during therapy	At beginning of each course and for any signs of hepatic injury			Annual inactivated influenza
Efalizumab	BL		BL and annually	BL standard vaccinations*
BL	Every 2-6 mo			Annual inactivated influenza†
Monthly × 3-6 mo then every 3 mo				
Etanercept	BL	BL optional	BL and annually	BL standard vaccinations*
BL	Every 2-6 mo			Annual inactivated influenza
Every 2-6 mo				
Infliximab	BL	BL optional	BL and annually	BL standard vaccinations*
BL	Every 2-6 mo			Annual inactivated influenza
Every 2-6 mo				

These are based on review of the literature and survey of practitioners with expertise in the use of biologic agents. Note that there was variation in the frequency and type of tests ordered by those participating in the consensus conference, and these tests and vaccinations should, therefore, not be viewed as mandatory.

ANA, Antinuclear antibodies; *BL*, baseline (before initiating therapy); *CBC + Plt*, complete blood cell count and platelets; *LFTs*, liver function tests; *TB*, tuberculosis.

*When practical.

†Package insert advises against vaccines in patients taking efalizumab based on data demonstrating a reduction in antibody response to vaccination. Nevertheless, a sizeable minority of medical advisors recommend annual inactivated flu vaccines for patients taking efalizumab. The benefits and risks of vaccination in patients treated with efalizumab have not been established.

Immunizing patients with systemic lupus erythematosus: a review of effectiveness and safety

LES

SG O'Neill* and DA Isenberg
Centre for Rheumatology, University College London, London, UK

Lupus (2006) 15, 778–783
www.lupus-journal.com

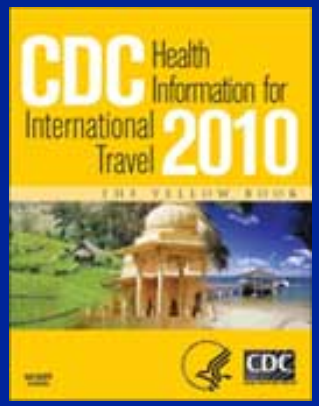
Table 1 Common vaccinations, rated according to evidence

Vaccine	*Type(s)*	*Evidence of efficacy in SLE*	*Evidence of safety in SLE*	*Concerns/comments (CI=contraindicated)*
BCG	Live attenuated	0	0	CI if immunosuppressed
Diptheria	Toxoid	0	0	
Haemophilis influenza B	Conjugate	++	++	
Hepatitis A	Inactivated	0	0	
Hepatitis B	Component (recombinant DNA)	−	+	?Decreased efficacy
Influenza	Inactivated component	++	++	A-β2-GPI antibody titre increases
MMR	Live attenuated	0	+	CI if immunosuppressed
Meningococcus	Component polysaccharide	0	0	
	Conjugate	0	0	
Pertussis	Inactivated whole cell	0	0	
	Component	0	0	
Pneumococcus	Component polysaccharide	++	+++	Significant minority do not respond
	Conjugate	0	0	
Polio	Live attenuated oral	0	+	CI if immunosuppressed
	Inactivated injection	0	0	Available in some countries
Tetanus	Toxoid	+++	+++	
Typhoid	Live attenuated oral	0	0	CI if immunosuppressed
	Component polysaccharide injection	0	0	?Less effective
Varicella	Live attenuated	0	0	CI if immunosuppressed
Yellow fever	Live attenuated	0	0	CI if immunosuppressed

+/− or 0 represents our overall impression from weighing up published series of the degree of evidence for or against the vaccines use in SLE. 0 = no evidence available, +/− = some evidence for or against through to +++/−−− = strong evidence for or against.

Multiple Sclerosis

- "The ACIP's advice for the **normal use of all live-virus as well as killed vaccines** in multiple sclerosis (MS) patients who are not undergoing a current exacerbation of disease is reinforced by the National MS Society (www.nationalmssociety.org/Sourcebook-vaccinations.asp), a source well respected by MS patients and their physicians.
- In the past, many practicing neurologists have strongly advised their MS patients against the use of live-virus vaccines at any time. If possible, MS patients should not receive any vaccine for 6 weeks after the onset of a disease exacerbation. Immunomodulatory agents commonly used in MS patients, such as interferons and glatiramer acetate, are not thought to affect vaccine response or safety, but definitive data are lacking.
- In these special circumstances, travel health advisors should confer with the traveler's other physicians in developing an appropriate plan."



Content

1. Inflammatory diseases & Immunomodulatory drugs
2. Efficacy and safety of a vaccine
3. Travel medicine
4. Which vaccines for adults ?
5. Which vaccines are recommended in immunocompromised patients with immune mediated inflammatory diseases
6. Timing of vaccination
7. Live vaccines : prototype Yellow fever vaccine; Measles; Zoster
8. Measurement immune status & Serologic control

Timing of vaccination

Avoid periods of intense immunosuppression

Best **before** the start of immunomodulator therapy * :

- Better immunogenicity (i.e MTX)
- No contraindication in case of live vaccines

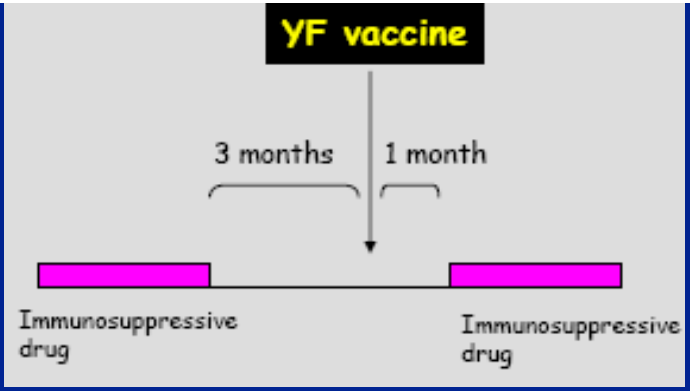
Patient today = traveler tomorrow

* Consideration could reasonably be given to a vaccination programme at diagnosis of **inflammatory bowel disease**, since

•80% of patients will be treated with corticosteroids,
•40% with thiopurines
•20% with anti-TNF therapy

HP Brezinschek et al., Curr Opin Rheumatol 2008;20:295-299
JF Rahier et al., JCC 2009(in press)
British Society for Rheumatology 2002,
http://rheumatology.org.uk/guidelines/guidelines_other/vaccinations/view
M Lebwohl et al., J Am Acad Dermatol 2008;58 (1):94-105

Timing of vaccination



For live vaccine, if possible to interrupt temporarily the **IMs**

- How long to wait before vaccine administration : "**3 months**" (corticosteroids : **1** month) (infliximab **6** mo ?) (etanercept **2** mo ?) (leflunomide longer ? if at all)

  ? « pharmacologic halflife ← → biologic activity »

- How long to wait to restart drug after the vaccination : "**3 weeks" (….. 2-4)**

  ? « duration of the viremia; virus still present somewhere in the body ?»

HP Brezinschek et al., Curr Opin Rheumatol 2008;20:295-299
JF Rahier et al., JCC 2009(in press)
British Society for Rheumatology 2002,
http://rheumatology.org.uk/guidelines/guidelines_other/vaccinations/view
M Lebwohl et al., J Am Acad Dermatol 2008;58 (1):94-105

Timing of vaccination

En France

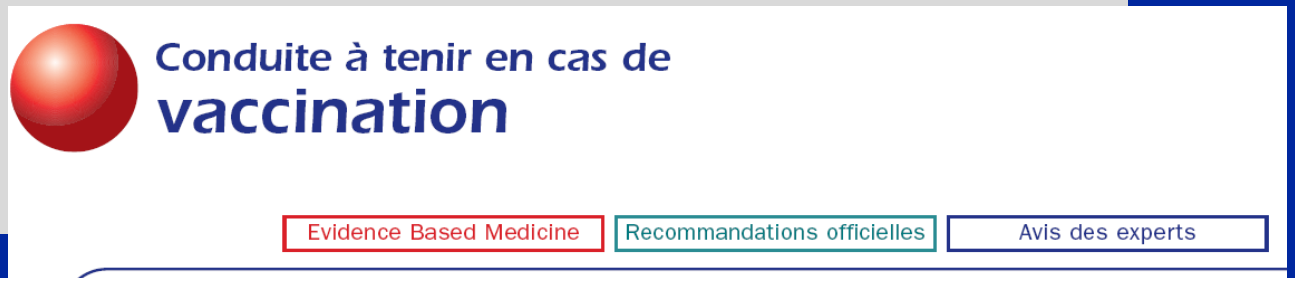
http://www.cri-net.com/recherche/fichesPratiques/french/CH3c.pdf

Il est aussi souhaitable de vérifier si le patient est susceptible de se rendre à court ou moyen terme dans un pays ou la vaccination anti-amarile est obligatoire.

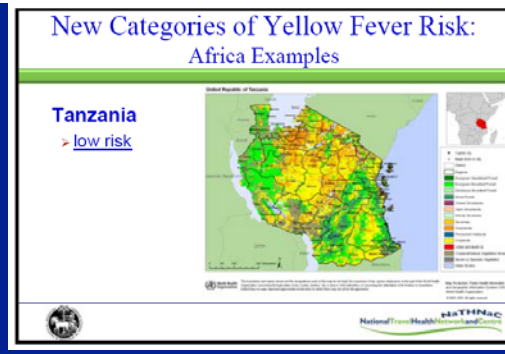
Si tel est le cas, la vaccination, efficace pendant 10 ans, doit être effectuée dans un centre agréé **au moins 3 semaines** avant de débuter la biothérapie.

Il faut cependant noter qu'aucune étude spécifique n'a été consacrée à ce sujet." et

"le délai de reprise du traitement anti-TNFα après la vaccination sera **d'au moins 3 semaines** (période de réplication virale)."



38 Y - RA



CONSULTATION 20/10/2009

- Very short trip Tanzania for 3 days – 8-10/11/209
- Stopped Humira & Ledertrexate 5 weeks

QUID

- needs 3 months ? 8 weeks ? 10 weeks ? – but if vaccination on 28/10 = only 7 weeks
- To vaccinate 10 days before departure ? To short ?
- No restart medication before departure !!
- Tanzania = low risk area; strict daytime antimousquito measures ?
- Idem & vaccination after return, to be safe for the future ?

SHARED / INFORMED DECISION

Content

1. Inflammatory diseases & Immunomodulatory drugs
2. Efficacy and safety of a vaccine
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4. Which vaccines for adults ?
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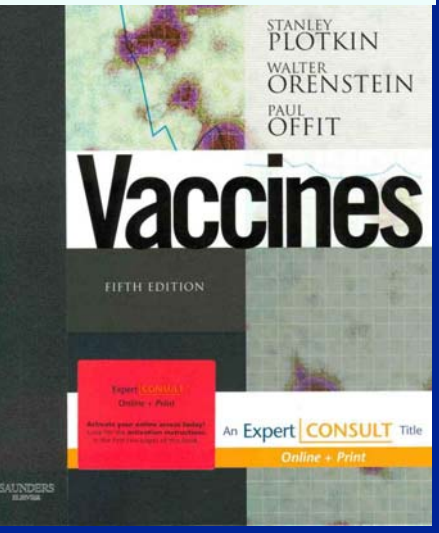
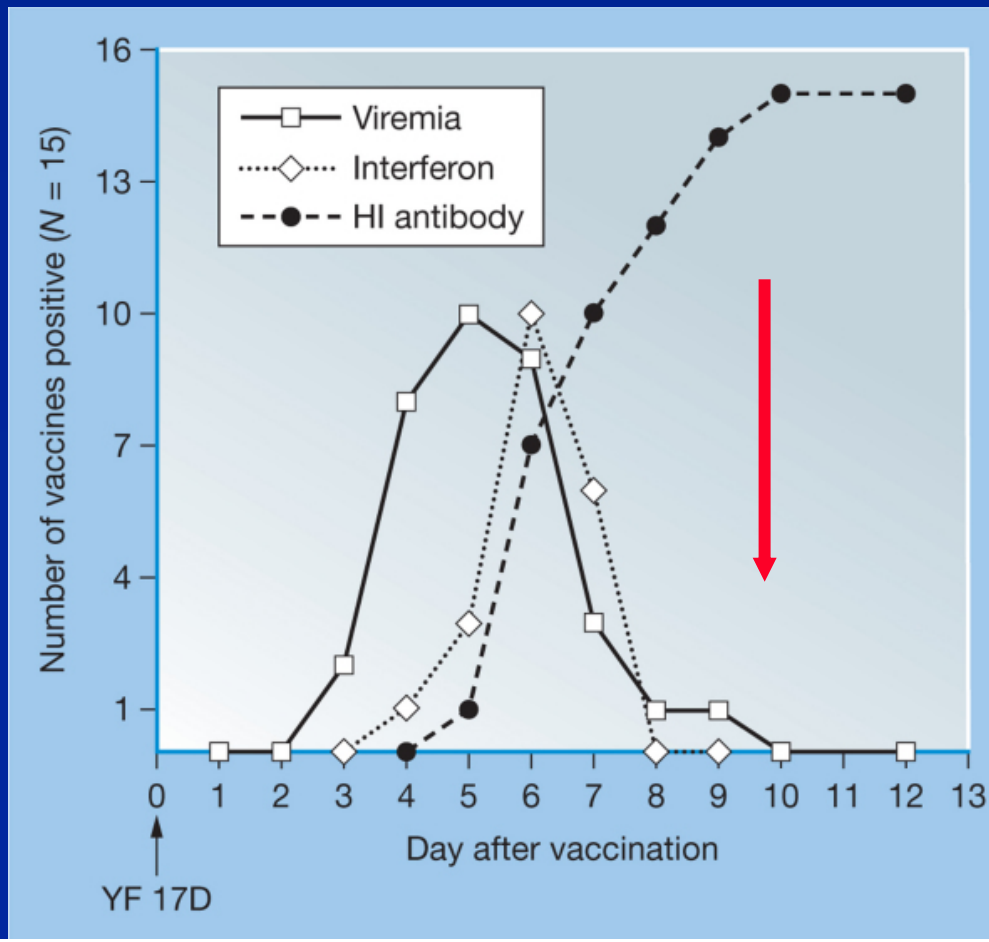
7. Live vaccines : prototype Yellow fever vaccine; Zoster
8. Measurement immune status & Serologic control

Chapter 36
MONATH et al.



Live vaccines - YELLOW FEVER

Figure 36-6 - **Circulating virus**, interferon and hemagglutination-inhibiting (HI) antibodies, adults inoculated with yellow fever 17D vaccine. *(Modified from Wheelock EF, Sibley WA.)*



… *Duration of immunity* …

…..these observations, as well as the prolonged synthesis of IgM antibodies in persons immunized with 17D virus ***suggest that chronic persistent infection or storage of antigen in vivo, possibly in follicular dendritic cells***, might explain the durability of the human immune response.

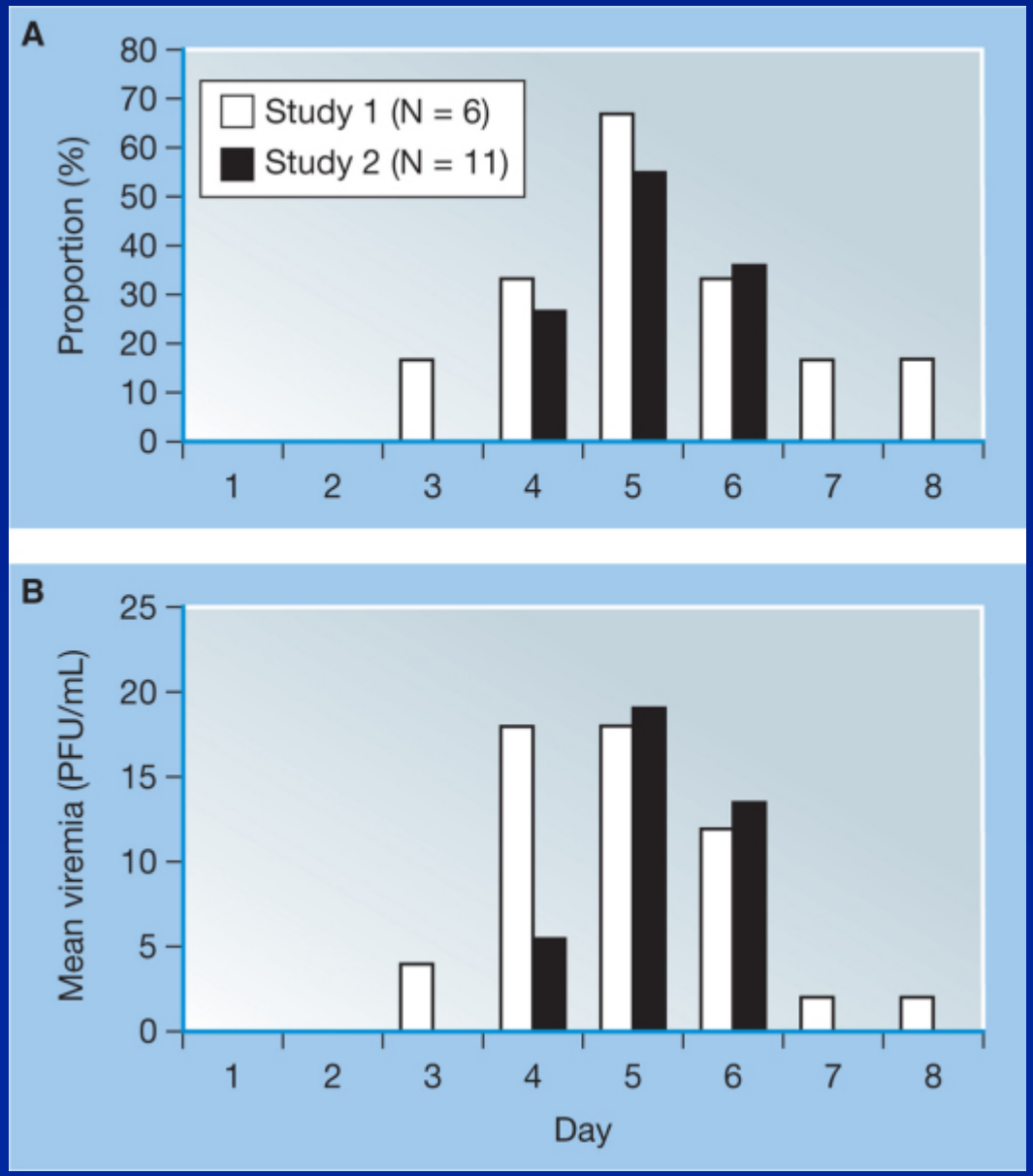


Figure 36-20

A: Proportion of healthy adults in two studies with viremia detectable by plaque assay following inoculation of yellow fever 17D vaccine (YF-Vax®).

B: Mean viremia levels in the same studies. Viremia occurred principally between days 4-6 and did not exceed 2log10 PFU/mL in and subject.

(Data from Monath TP, McCarthy K, Bedford P, et al. and an unpublished study.)

Live vaccines - YELLOW FEVER

not recommended for immunocompromised individuals

- **Complications**
  - Risk of complications based on **theorical grounds**:
    - **prolonged viremia** may increase the risk of neuroinvasion and encephalitis, and
    - **unrestrained virus replication** could enhance damage to the liver and other visceral organs.

Yellow Fever Vaccine-associated Neurotropic Disease (YEL-AND)

Yellow Fever Vaccine-associated Viscerotropic Disease (YEL-AVD)

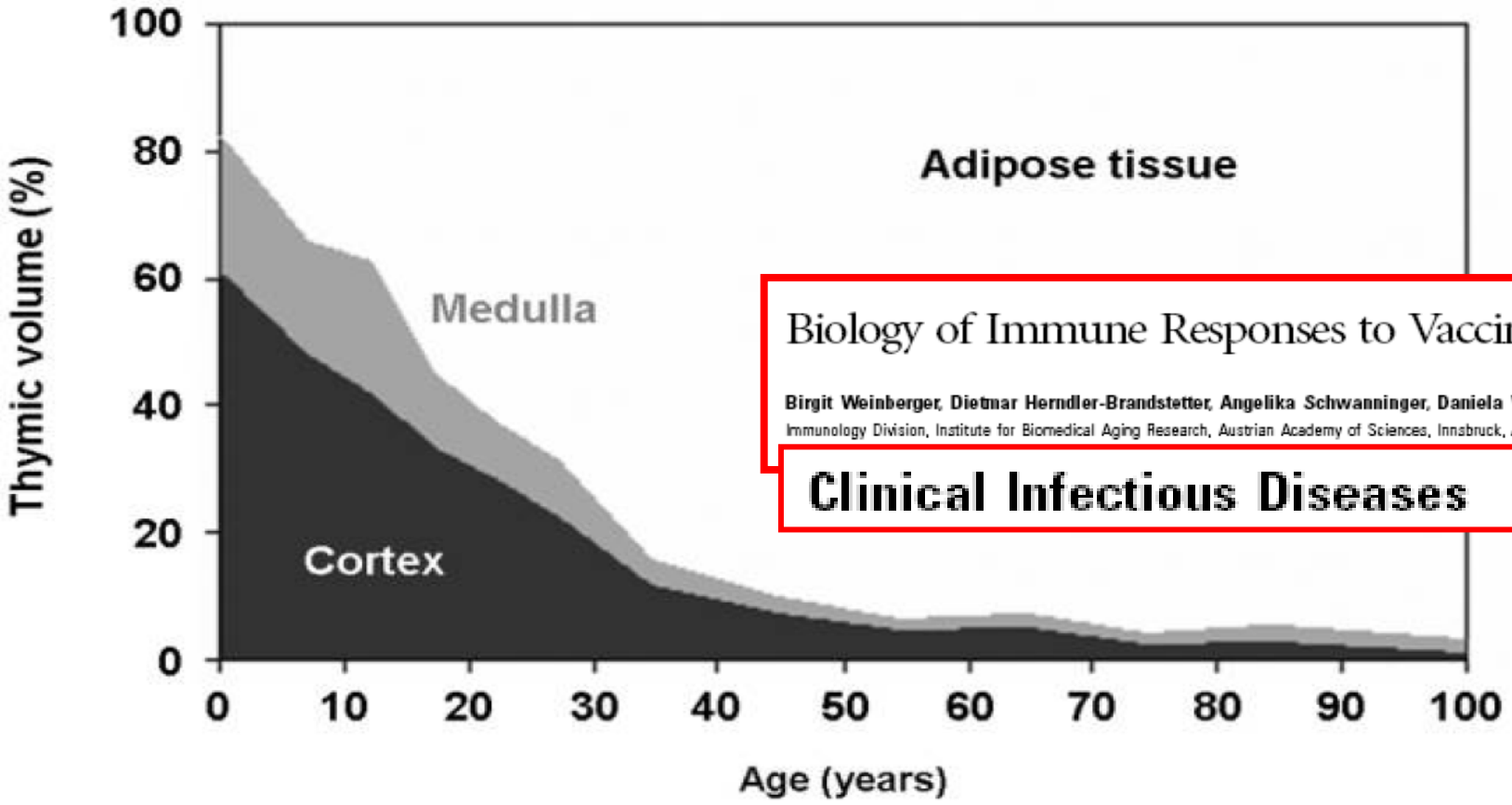
Tableau 1 **Principales caractéristiques des évènements indésirables graves post vaccination amarile**
Table 1 Main characteristics of serious adverse effects following yellow fever vaccination

EIG	YEL-AVD (1975-2006)	YEL-AND (1990-2006)
Nombre	36	28
Origine de 17D vaccins	Etats-Unis, Grande-Bretagne, France, Brésil et Chine	Etats-Unis, Grande-Bretagne et France[a]
Incidence[b] (Range / classes d'âge)	4 cas / 1 million doses (1,2-5,3)	5 cas / 1 million doses (1,8-6,3)
Incidence > 60 ans	22 cas / million doses	18 cas / million doses
Létalité	16/38 (H : 39,1 % ; F : 81,8 %)	1/28 (cas unique : sujet VIH positif ; CD4 < 200/ml)
Sex ratio H/F	2,1	3,0
Âge moyen de survenue	48,7 (4-79) H : 55,8 (4-76) ; F 32,6 (5-79)	43,2 (6-78) H : 43,2 (6-78) ; F 46,0 (17-68)
Délai d'apparition des symptômes	3,8 (2-8) H : 4,3 (2-8) ; F : 3,9 (2-5)	13,3 (3-27) H : 13,3 [3-27] ; F : 10,7 (6-16)
Facteurs de risque	Age Maladie du thymus	Age
Remarques	Primo-vaccination[c] Susceptibilité génétique de l'hôte ? Association à d'autres vaccins ? Absence de réversion du virus isolé	Primo-vaccination
Causalité	Non déterminée actuellement	

[a] Des cas de YEL-AND rapportés au Brésil en cours d'exploration [b] Pays ayant notifié des cas [c] Un cas français avec symptômes de YEL-AVD après revaccination en cours d'exploration

!! PRIMOVACCINATION !!

BEH thématique 25-26 / 19 juin 2007



THYMIC VOLUME

vs

AGE

Biology of Immune Responses to Vaccines in Elderly Persons

Birgit Weinberger, Dietmar Herndler-Brandstetter, Angelika Schwanninger, Daniela Weiskopf, and Beatrix Grubeck-Loebenstein
Immunology Division, Institute for Biomedical Aging Research, Austrian Academy of Sciences, Innsbruck, Austria

Clinical Infectious Diseases 2008; 46:1078–84

Figure 2. Schematic representation of the age-dependent involution of functional thymic tissue. The volume of functional thymic tissue (cortex and medulla) progressively declines during aging and is replaced by adipose tissue. Data are from [29].

29. Steinmann GG, Klaus B, Muller-Hermelink HK. The involution of the ageing human thymic epithelium is independent of puberty: a morphometric study. Scand J Immunol **1985**; 22:563–75.

Live vaccines - YELLOW FEVER

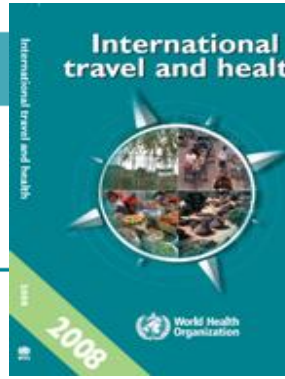
not recommended for immunocompromised individuals

- **Complications**
  - **Few** severe complications attributable to inadvertent immunization of immunocompromised individuals with YF vaccine **has been reported** -- but experience is limited
  - One single instance of fatal encephalitis following vaccination of HIV infected patient: undiagnosed HIV infection who has a low CD4 count (108 cells/mm^3) and who developed YEL-AND and died of meningoencephalitis (Kengsakul et al. 2003)
- **Immune response to vaccine**
  - The effect of vaccination in immunosuppressed individuals has not been elucidated, but most reports suggest **inadequate antibody response** rather than safety concerns

YELLOW FEVER

risk assesment

2008



Vaccine	Possible adverse reaction per million doses	Expected rate[a]
Yellow fever	Encephalitis (<6 months)	500–4 000
	Allergy/anaphylaxis	5–20
	Viscerotropic disease	0.04–3
		20 for vaccinees above 60 years of age

!! PRIMOVACCINATION !!

- **the risk of a serious side effect due to vaccination**
  (varying from **1 (***or much less)* **to 20 – 40 / 1.000.000** depending on age)

is on average lower than

- **The risk of death caused by Yellow Fever in an endemic area**
  (varying from **20 to 1600 / 1.000.000** per month)

HIV patients: seroconversion

- Seroconversion rates after YF vaccination among asymptomatic HIV-infected persons: data are limited, but indicate that the seroconversion rate among such persons may be reduced
  - 3/18 children (Sibailly 1997)
  - 27/31 adults (Goujon 1995)
  - 12/12 adults (Tattevin 2004)

Yellow fever vaccine is safe and effective in HIV-infected patients

Pierre Tattevin[a], Agnès Geremy Depatureaux[a], Jean Marc Chapplain[a], Mathieu Dupont[a], Faouzi Souala[a], Cédric Arvieux[a], Jean Dominique Poveda[b] and Christian Michelet[a]

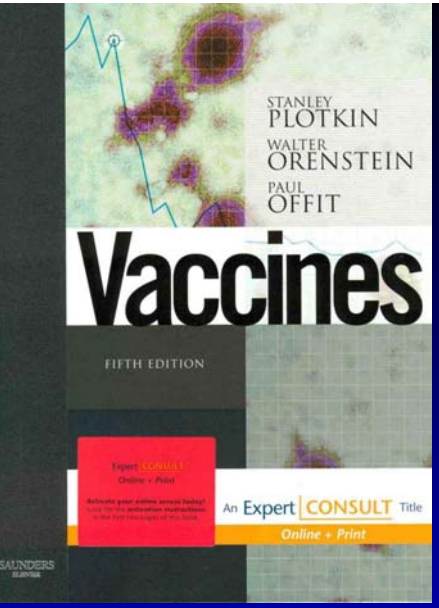
Table 1. Characteristics and follow-up data for 12 consecutive HIV-infected patients who received yellow fever vaccination.

Age (years)	HIV diagnosis	HIV stage (CDC 1993)	CD4/CD8 before/after YF vaccine Number/mm³ (time since YF vaccine)		Viral load before/after YF vaccine Copies/ml (time since YF vaccine)		YF neutralizing antibodies UI/l (time since YF vaccine)	Anti-retroviral treatment	Intolerance to YF vaccine
34	1991	A	345/795	240/840 (30 days)	< 200	< 200	40 (48 months)	Yes	No
49	1998	A	430/440	369/378 (40 days)	< 20	< 200 (40 days)	40 (20 months)	Yes	No
50	1998	A	805/1104	629/748	1120	284 (22 days)	80 (20 months)	Yes	No
35	1995	C	nd	nd	nd	nd	80 (60 months)	Yes	No
43	1988	A	1300/754	1523/1267	< 20	< 20 (30 days)	20 (4 months)	Yes	No
41	1997	A	360/846	357/833 (120 days)	31 100	23 700	40 (2 months)	No	No
35	2000	A	375/660	376/485 (60 days)	5010	20 800	20 (2 months)	No	No
42	1991	C	409/1833	512/2048 (30 days)	< 20	< 20	40 (4 months)	Yes	No
35	1998	A	288/612	296/624	165	< 20	80 (15 days)	Yes	Yes
35	1999	A	nd	nd	nd	nd	40 (84 months)	Yes	No
22	1999	A	1056/1353	900/1320	8800	20 400	80 (2 months)	No	No
47	1990	B	240/1072	216/756 (40 days)	8320	21 300 (40 days)	80 (1 month)	Yes	No

CDC, Centers for Disease Control; YF, yellow fever.

We retrospectively studied 12 HIV-infected patients vaccinated with the 17D yellow fever (YF) strain. At vaccination, the mean CD4 cell count was 561 ± 363 cells/mm³. A neutralizing YF antibody response in serum was obtained in all patients. There were no significant changes in CD4 cell count or viral load compared with baseline. One patient reported transient fever and pharyngitis. YF vaccine appears safe and effective in HIV-infected patients with CD4 cell counts > 200 cells/mm³.

AIDS. 2004 Mar 26;18(5):825-7



Live vaccines - MEASLES

… ***Viremia ?*** …

- extremely low & shortliving – only in animal testing found - never detected in humans
- in 1 child virus on day 12 in conjunctival fluid

- *Quid in immunocompromised ?*

Live vaccines - Safety of Zoster vaccine

Therapy with low-doses immunomodulatory drugs for treatment of rheumatoid arthritis, psoriasis, polymyositis, sarcoidosis, inflammatory bowel disease, and other conditions including :

- methotrexate (<0.4 mg/Kg/week),
- azathioprine (<3.0 mg/Kg/day), or
- 6 mercaptopurine (<1.5 mg/Kg/day)

are not considered sufficiently immunosuppressive to create vaccine safety concerns and are not contraindications for administration of zoster vaccine. … with antiviral therapy should complications ensue.

Prevention of Herpes Zoster ; Recommendations of the Advisory Committee on Immunization Practices (ACIP); Recommendations and Reports June 6, 2008 / Vol. 57 / RR-5 Morbidity and Mortality Weekly Report www.cdc.gov/mmwr

Content

1. Inflammatory diseases & Immunomodulatory drugs
2. Efficacy and safety of a vaccine
3. Travel medicine
4. Which vaccines for adults ?
5. Which vaccines are recommended in immunocompromised patients with immune mediated inflammatory diseases
6. Timing of vaccination
7. Live vaccines : prototype Yellow fever vaccine; Zoster
8. Measurement immune status & Serologic control

Measurement degree / kind of immunodepression ! ?

- CD4 / 8 ?

Serologic control ! ?

- Hep A
- Hep B
- Rabies
- (TBE = not routinely available)
- (Yellow fever = not routinely available)

Hoge Gezondheidsraad

Conseil Supérieur de la Santé

VACCINATIEGIDS

	A1	A1	B1	B2	C	D1	D2
VACCINATIES	Hiv < 200	Hiv 200-500	**Transplantatie van vaste organen (SOT)** hart, lever, nier, pancreas, long	**Transplantatie bij hematologische problemen**	**IMID Immuungemedieerde inflammatoire aandoeningen** (lijst geneesmiddelen zie verder)	**Oncologie – haematologie** & invloed chemotherapie (& radiotherapie)	**Oncologie chemotherapie** & invloed chemotherapie (& radiotherapie)
GEINACTIVEERDE VACCINS							
- dT, dT-IPV, dTpa			S	R1			
- Haemophilus influenzae b			S	R1			
- hepatitis A			S (R?)	S (R?)			
- hepatitis B			R1	R1			
- Influenza			R	R2			
- IPV			S	R1			
- Pneumo			R2	R2			
LEVENDE VACCINS							
- MMR			X	X3			
REISGERELATEERDE							

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