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Vaccination after Solid Organ Transplantation

Eric Goffin
Université catholique de Louvain
Cliniques Universitaires St Luc
Bruxelles, Belgique



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Vaccination after Solid Organ TP

- Background
- Rationale
- Inactivated vaccines
- Contra-indicated vaccinations
- Conclusions


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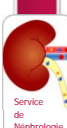
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Background

- Solid Organ Transplant : Kidney, Liver, Heart, Lung, Pancreas, Intestine, Combinations
- Usual maintenance immunosuppression (> 6 post TP month)
 - ✓ Tacrolimus
 - ✓ Mycophenolate mofetil
 - ✓ Steroids
 - ✓ Induction therapy (ATG – anti IL2R)
- Acute rejection rates < 15 % (90 % < 3 post TP month)
- The price to pay
 - ✓ Increased incidence of viral infections
 - ✓ Increased incidence of opportunistic infections
 - ✓ Increased incidence of cancer
 - ✓ And so, profound immunodepression




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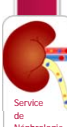


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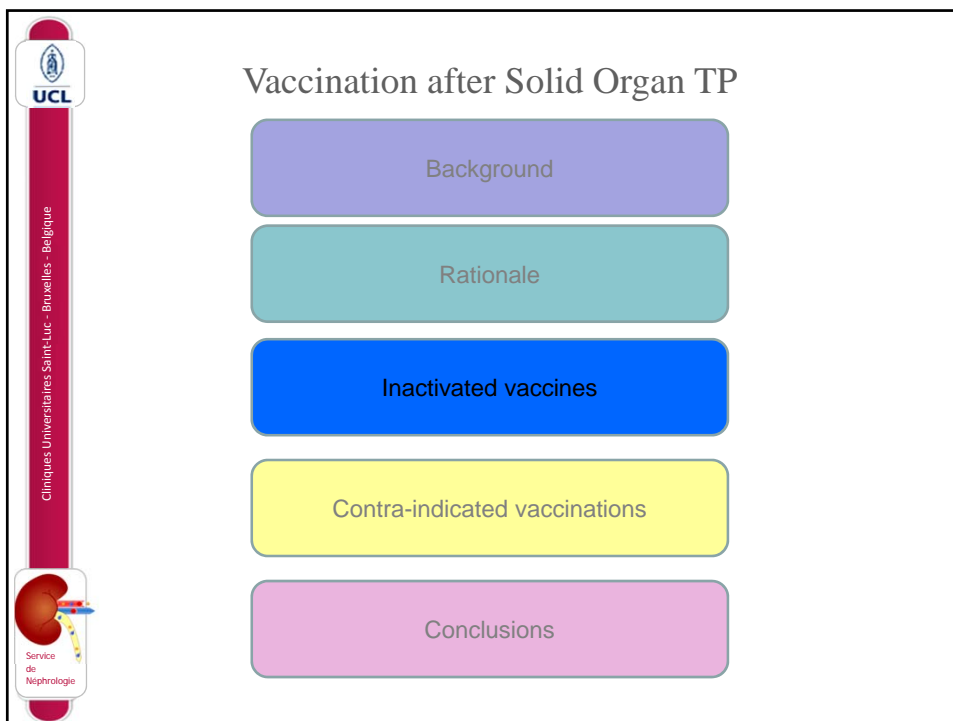
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Rationale



- Whenever possible, vaccines should be administered before TP (even before dialysis initiation for renal graft recipients)
- Little or no harm has been described with the use of inactivated vaccines
- Most vaccines produce an antibody response, albeit diminished
- The potential benefits of vaccination with inactivated vaccines outweigh the harm of immunization
- Serious infection can result from live vaccines
- Vaccinations are more likely to be effective when immunosuppression is the lowest (> 6 post TP months)

Cohn J & Blumberg EA Nature Clin Pract Nephrol 2009 ; 5 : 46-53
Am J Transpl 2009; 9 (Suppl 3) : S41-43
Bally et al Nephrol Ther 2009; 5 : 265-79
Avery RK & Michaels M Am J Transplant 2008 ; 8 : 9-14



Inactivated vaccines

- Limited number of studies available
- No evidence that vaccination lead to an increased risk of rejection
 - Common practice is to propose vaccination > 6 post TP months (except for Influenza)
- Response to post TP vaccination is diminished compared to immunization prior TP
 - **Optimal timing for vaccination is prior TP**
- Repeated vaccinations post TP are often necessary
- Vaccination of relatives and family members should not be forgotten






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Recommended vaccines

- Diphtheria-pertussis-tetanus *
- Haemophilus influenza (children <16 y.o. *)
- Hepatitis A (for travel, occupational and liver Tp candidates, HBV,HCV)
- Hepatitis B *
- Pneumococcal (children <16 y.o. *)
- Inactivated polio *
- Influenza
- Meningococcus * (adults : administer if patient is at high risk)
- Typhoid Vi (for travel in at-risk areas)
- HPV *

* Standard vaccination

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Diphtheria – Pertussis- Tetanus Vaccination

- Immunity in adults SOT good for tetanus; less for diphtheria
- Waning of antitoxin titers after TP
- Good response to booster vaccines, mainly for tetanus (~100 %) ; less for diphtheria : 89 % after the booster, 62 % at one year
Huzly D et al Transplantation 1997 ; 63 : 839-45
- Post TP Recommendation :
 - ✓ Immunization : single booster ; booster interval : 10 years (shorter intervals if travel ; monitoring of titers !)
 - ✓ No immunization : 3 series – interval between doses : 4 weeks, 6-12 months after second dose ; booster interval : 10 years (shorter intervals if travel ; monitoring of titers !)

Stark K et al Lancet 2002 ; 359 957-65

Cohn J & Blumberg EA Nature Clin Pract Nephrol 2009 ; 5 : 46-53



Bally et al Nephrol Ther 2009; 5 : 265-79

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Inactivated polio


- Immunity in adults SOT good for polio
- Good response to vaccine, similar to healthy controls
 - Huzly D et al Transplantation 1997 ; 63 : 839-45*
 - Balloni A et al Vaccine 1999 ; 17 : 2507-11*
- Repeat immunization every 5 to 10 yrs ; mainly if travel in high-risk areas
 - Bally et al Nephrol Ther 2009; 5 : 265-79*
 - Stark K et al Lancet 2002 ; 359 957-65*
 - Cohn J & Blumberg EA Nature Clin Pract Nephrol 2009 ; 5 : 46-53*
 - Huzly D et al Transplantation 1997 ; 63 : 839-45*


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Influenza vaccination

- Can cause significant morbidity and mortality in SOT recipients
- Responsible for up to 42 % of upper and 48 % of lower respiratory tract infections in SOT recipients
 - Kumar D et al Lancet Infect Dis 2010; 10 : 521-6*
 - Gottlieb J et al Transplantation 2009 ; 87 : 1530-7*
- 1 to 4 % of SOT infected annually
 - Ison MG et al J Heart Lung Transplant 2008; 27 : 282-8*
 - Vilchez RA et al Am J Transplant 2002; 2 : 287-91*
- Risk of surinfection (bacterial and fungal) – Acute hepatitis in liver TP
 - Rubin RH Transplant Infect Dis 2002 ; 175-6*
 - Duchini A et al Liver Transplant 2000 ; 6 ; 531-42*
- In lung recipients, influenza may mediate acute allograft rejection and bronchiolitis obliterans syndrome
 - Vilchez RA et al Am J Transplant 2002; 2 : 287-91*
 - Khalifah AP et al Am J Respir Crit Care Med 2004; 170 : 181-7*




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Influenza vaccination

- Variability in response to vaccine, ranging from 15 to 93 %
 - Reviewed in *Kumar D et al Am J Transplant 2011; 11 : 2020-30*
 - Cordero E et al Transplantation 2012 ; 93 : 847-54*
 - ✓ Lower response in lung recipients
 - ✓ Higher response in long-term renal recipients
 - ✓ Efficacy superior in paediatrics
- > 1 post-TP month (mainly if SOT recipient has received induction therapy)
- **Recommendation** : yearly vaccination before start of influenza season
- Strategies to improve response
 - ✓ Intradermal administration ?
 - ✓ Additionnal doses ?
 - ✓ Use of adjuvants ?

Bally et al Nephrol Ther 2009; 5 : 265-79
Kumar D et al Am J Transplant 2011; 11 : 2020-30
Stark K et al Lancet 2002 ; 359 957-65
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H1N1 vaccination

- Variability in response to vaccine
 - ✓ Vaccination in 21 controls, 53 HD pts and 11 Renal Tp pts
 - ✓ Sampling before and one month after a single dose of Pandremix vaccine
 - ✓ Proportion of responders : 90 % for controls, 57 % for HD and 44 % for renal TP pts

Broeders NE et al Clin J Am Soc Nephrol 2011 ; 11 : 2573-8




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Hepatitis B

- Still remains a matter of concern in SOT : infection is severe under IS and disease likely to become chronic in SOT (renal and liver)
- Cost of Ig (liver TP) and anti-viral drugs – emergence of resistance
- Post-TP vaccination yields a low response : 32-36 % of kidney graft recipients after the 40 ug four-dose schedule ; 7 to 23 % after liver TP
 - Bruguera M et al Vaccine 1990 ; 8 : S47-S49*
 - Loinaz C et al Hepatogastroenterol 1997 ; 44 : 235-36*
 - Chalasanani N et al Liver transplant surg 1998 ; 4 : 128-32*
- Vaccination prior dialysis initiation in patients with renal failure ; on waiting lists for all
 - Bally et al Nephrol Ther 2009; 5 : 265-79*
 - Kumar D et al Am J Transplant 2011; 11 : 2020-30*
 - Stark K et al Lancet 2002 ; 359 957-65*
 - Cohn J & Blumberg EA Nature Clin Pract Nephrol 2009 ; 5: 46-53*

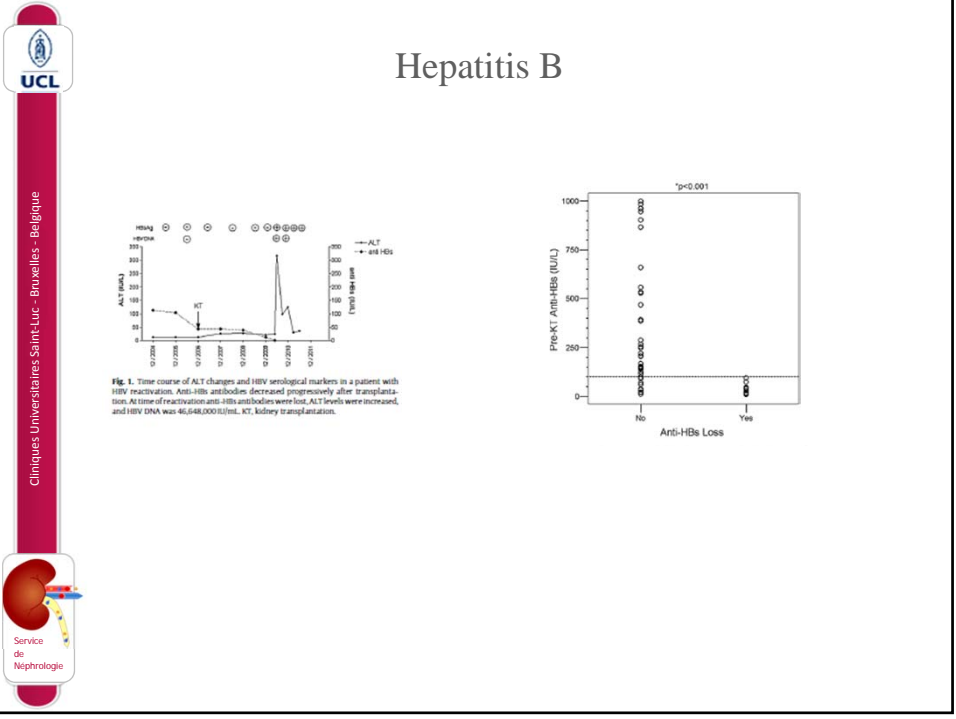


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Hepatitis B

- Level of immune protection ? Acute HBV infection reported in vaccinated patients with low ab titers or rapidly decreasing titers
 - Goffin E et al Lancet 1995 ; 345 : 263*
 - Cohn J & Blumberg EA Nature Clin Pract Nephrol 2009 ; 5: 46-53*
- Significant rate of HBV reactivation in patients with anti-HBc ab and low or undetectable anti-HBs ab
 - Renal TP at St Luc between 1/1995 and 12/2007 : 764 → 93 pts with resolved HBV infection
 - Graft was negative for HBV infection
 - HBsAg reversion occurred in 6 pts ; one pt died during follow-up (sepsis)
 - Kanaan N et al J Clin Virol 2012 ; 55 : 233-8*



- Hepatitis B**
- Recommendations for non-immunized SOT patients
 - ✓ 3-4 (double ?) doses
 - ✓ Recommended schedule : month 0,1, (2), 6
 - ✓ Monitoring response after 6th dose ; additional dose recommended if anti-HBS ab < 10 IU/L
 - ✓ Regular monitoring of ab (eg every 12 months)
 - ✓ Booster doses necessary if ab < 10 IU/L and/or if ab titer decreases rapidly

 - Center practice
 - ✓ Maintaining anti-HBs ab > 100 IU/L
 - ✓ Idem in patients with resolved HBV infection

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Pneumococcal vaccine

- Pneumococcal infection cause pneumonia, bacteraemia and meningitis in SOD pts
- Risk of invasive pneumococcal disease 12.8 fold greater than in the general population

Kumar D et al Am J Transplant 2011; 11 : 2020-30
- Most SOT recipients develop titers (lower than in general population) : 83 and 80 % for 23-valent and conjugated vaccines, respectively

Ab titers decrease similarly with both types of vaccination
Kumar D et al 2003 J Infect Dis 187 : 1639-45

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Pneumococcal vaccine

- No enhanced immunogenicity after a prime-boost strategy (PCV-7) followed by PPV-23 (liver TP recipients)


Kumar D et al Clin Infect Dis 2008 ; 47 : 885-92
- Pneumovax 23 injection (14 serotypes) in 43 renal graft recipients ;


Ab measured before, and at 4 weeks
Response in all patients (increase from 9 (0-13) to 13 (3-14) in serotypes recognized)
Ab titers lower than in the general population (84 % of healthy controls)

Lindemann M et al Transplantation 2010 ; 90 : 1463-7

Decrease in ab titers less in younger pts, females, pts given CyA and if better renal function
Lindemann M et al Transplantation 2012 ; 94 : 50-6


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 **Pneumococcal vaccine** (ACIP recommendations – WWR Oct 2012)

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- Vaccine-naïve persons
 - ✓ A dose of PCV13 (Prevenar) first, followed by a dose of PPSV23 (Pneumovax) at least 8 weeks later
 - ✓ Subsequent doses of PPSV23 (5 years)
- Previous vaccination with PPSV23
 - ✓ One dose of PCV13 > 1 year after the last PPSV23 dose was received
 - ✓ Additional doses of PPSV23 no sooner than 8 weeks after PCV13 and at least 5 years after the most recent dose of PPSV23


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Contra-indicated vaccinations after TP

- Varicella zoster
- BCG
- Smallpox
- Live oral typhoid
- Measles (except during an outbreak ?)
- Mumps
- Rubella
- Oral polio
- Live Japanese B encephalitis vaccine
- Yellow fever



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Contra-indicated vaccinations after TP

- Live vaccines use
 - ✓ Attenuated viral strains
 - ✓ Strain thought to be less pathogenic
- Data on their use is limited raising therefore concerns about both the safety and efficacy of these vaccines in SOT recipients
- For experts, the risks outweigh the potential benefits
- Travel in areas where Yellow Fever is endemic is not advised ; if travel, certificate of vaccine contra-indication is required ; local protections !
- Pre-TP vaccination (e.g. Varicella)



Varicella (Medline search 1985-2011 : 56 renal TP adults with disseminated cutaneous or visceral VZH)

Kanaan N et al Transplant Proc 2012 ; 44 : 2814-7

Primary varicella versus reactivation

Parameters	Immunization N=13	No immunization N=19	P-value
Deaths n (%)	2 (15)	4 (21)	0.99
Visceral complication n (%)	4 (31)	5 (26)	0.99
Initial symptoms n (%)			
Skin	6 (75)	15 (100)	0.11
Fever	2 (25)	4 (27)	0.99
Gastrointestinal	2 (25)	6 (40)	0.66
Neurologic	1 (13)	0 (0)	0.35

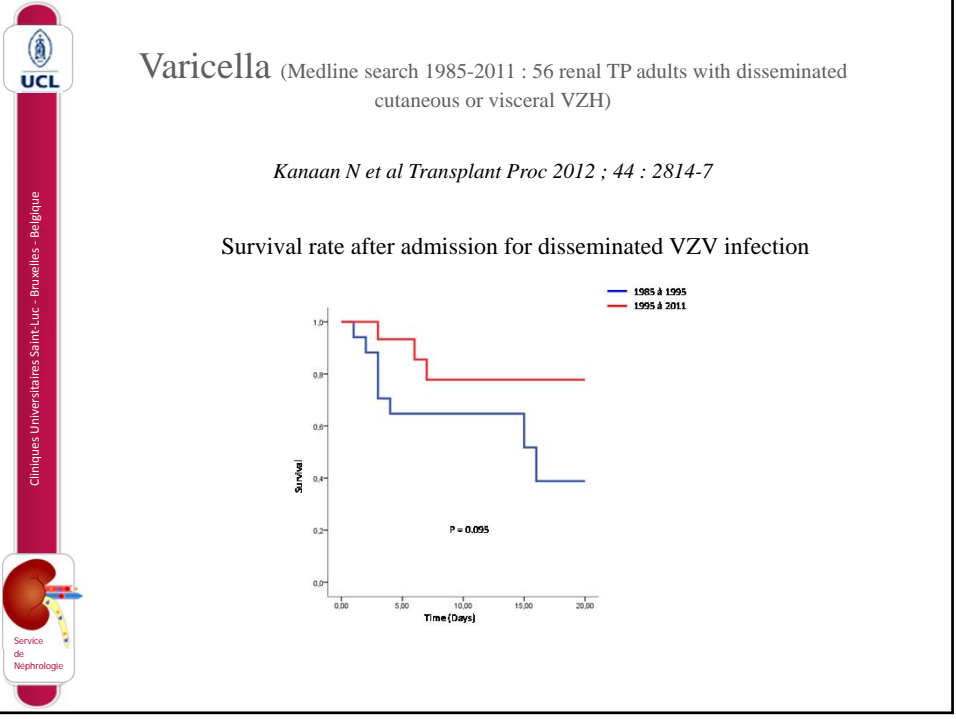


Varicella (Medline search 1985-2011 : 56 renal TP adults with disseminated cutaneous or visceral VZH)


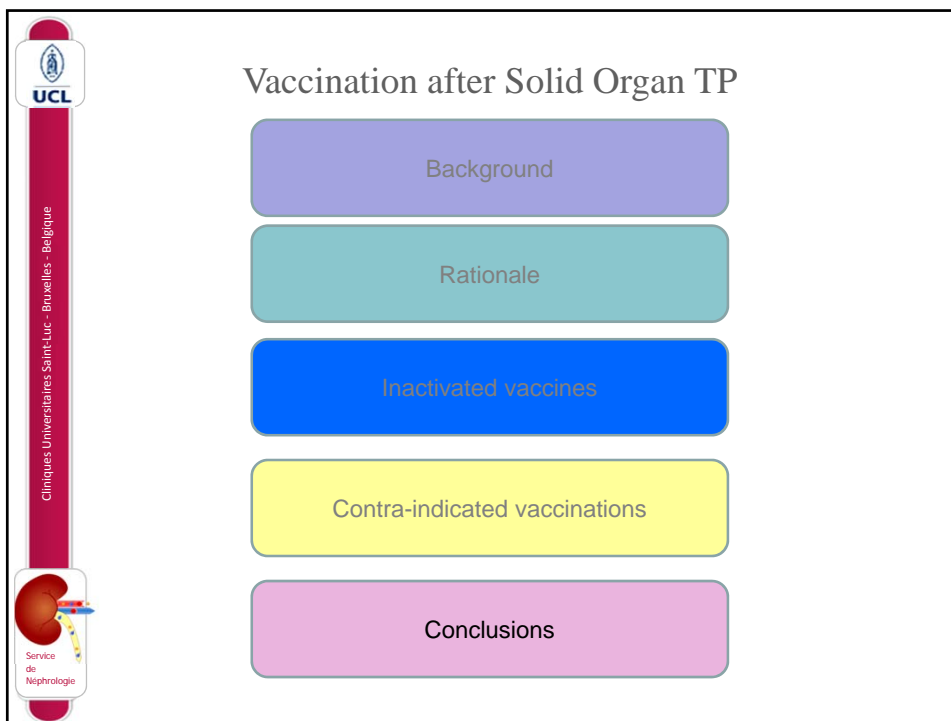
Kanaan N et al Transplant Proc 2012 ; 44 : 2814-7

Risk factor for mortality


Parameters	Alive N=39	Dead N=17	P-value
Age Mean (SD) (years)	38 (15)	31 (11)	0.07
Visceral complication n (%)	23 (59)	17 (100)	0.002
VZV IgG serostatus preTP n (%) (n = 32)	11 (42)	2 (33)	0.69
Induction treatment n (%)	3 (8)	1 (6)	0.81
Immunosuppression reduction n (%)	26 (67)	7 (41)	0.08
Tacro vs cyclo n (%) (n=36)			
Cyclo	22 (73)	4 (67)	0.74
Tacro	8(27)	2 (33)	
Aza vs MMF n (%) (n = 43)			
Aza	9 (30)	11 (85)	0.001
MMF	21 (70)	2 (15)	
Steroids n (%) (n=52)	34 (92)	15 (100)	0.26
Tritherapy vs bitherapy n (%) (n=52)			
Tritherapy	23 (62)	5 (33)	0.06
Bitherapy	14 (38)	10 (67)	
Bitherapy with aza	6 (43)	8 (80)	0.07
Rejection n (%)	7 (18)	5 (29)	0.34
Treatment Immunoglobuline n (%)	3 (8)	1 (6)	0.69
Antiviral Treatment n (%) (n = 55)	38 (97)	15 (88)	0.2
Time between TP and onset of varicella (y) Median [P25-P75] (n=45)	1.8 [0.5 - 6.3]	4.0 [3.0 - 9.0]	0.04
Time between onset of symptoms and treatment (days) Median [P25-P75] (n=35)	3.0 [1.0 - 4.0]	2.5 [2.0 - 3.0]	0.93



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- ## Varicella vaccine prior TP
- 64 % seroconversion rate in adults on dialysis
Buttery JP & Moxon ER Lancet 2000 ; 355 : 1930
 - Vaccination in seronegative infants results in fewer (12 vs 45 %) and milder episodes after renal TP compared with no vaccination (n: 704 pts – observational study)
62 % ab at one year and 42 % after 10 yrs
Broyer M et al Pediatrics 1997; 99 ; 35-39



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Conclusions

- Inactivated vaccinations schedules should be respected in Solid Organ Transplant candidates ; vaccinations while on waiting list better than after TP
- Good evidence to encourage post-TP Influenza and Pneumococcal vaccinations
- Travel vaccinations : hepatitis A, polio and typhoid, meningoccal vaccines
- Hepatitis B :
 - ✓ Repeated booster if anti-HBs ab < 100 UI/L
 - ✓ And in pts with resolved HBV infection who lost their anti-HBs ab
- Varicella vaccine prior TP in pts without ab