ERTAIN Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative

Vaccinations pre- and posttransplant

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Background

- Increased risk of both common and opportunistic infections after Tx due to immunosuppressive therapy
- Course of infections often more severe after Tx
- Protection against many infections by vaccinations pre-transplant available, for some pathogens also by post-transplant vaccinations
- Vaccination response depends on type and intensity of immunosuppressive treatment
- Few data available on vaccination and immunisation status in paediatric RTx

Few Retrospective Studies in Small Patient Cohorts

Vaccination Status of Children Considered for Renal Transplant: Missed Opportunities for Vaccine Preventable Diseases

Gurkan Genc,[1] Ozan Ozkaya,[1] Canan Aygun,[2] Yarkin Kamil Yakupoglu,[3] Hulya Nalcacioglu[4]

n = 51

Pediatr Transplantation 2008: 12: 432–435

Pediatric Transplantation
DOI: 10.1111/j.1399-3046.2007.00820.x

Evaluation of the vaccination status in pediatric renal transplant recipients

Chaves TSS, Pereira LM, Santos S De S, David-Neto E, Lopes MH. Evaluation of the vaccination status in pediatric renal transplant recipients.
Pediatr Transplantation 2008: 12: 432–435. © 2008 Blackwell Munksgaard

T. S. S. Chaves[1], L. M. Pereira[2], S. De S. Santos[1], E. David-Neto[2] and M. H. Lopes[1]

n = 46

Pediatr Transplantation 2007: 11: 73–76

Pediatric Transplantation
DOI: 10.1111/j.1399-3046.2006.00602.x

Demand for evaluation of vaccination antibody titers in children considered for renal transplantation

Prelog M, Pohl M, Ermisch B, Fuchshuber A, Huzly D, Jungraithmayr Th, Forster J, Zimmerhackl LB. Demand for evaluation of vaccination antibody titers in children considered for renal transplantation.
Pediatr Transplantation 2007: 11: 73–76. © 2007 Blackwell Munksgaard

M. Prelog[1], M. Pohl[2], B. Ermisch[2], A. Fuchshuber[2], D. Huzly[3], Th. Jungraithmayr[1,2], J. Forster[2] and L. B. Zimmerhackl[1]

n = 35

Country-specific Vaccination Schedules

Vaccine	Germany	United Kingdom	Turkey	Bulgaria	Russia	China
Tetanus	+	+	+	+	+	+
Diphtheria	+	+	+	+	+	+
Pertussis	+	+	+	+	+	+
Poliovirus (IPV)	+	+	+	+	+	+
Hepatitis B	+	+	+	+	+	+
HiB	+	+	+	+	+	-
Pneumococcal	+	+	+	+	-	-
Meningococcal	+	+	-	-	-	+
MMR	+	+	+	+	+	+
Varicella	+	-	+	-	-	-
HPV	+	+	-	-	-	-
Hepatitis A	-	-	+	-	-	+
BCG	-	-	+	+	+	+

www.who.int

Vaccination Recommendations for Paediatric Transplant Recipients

European Best Practice Guidelines for Renal Transplantation

EBPG Expert Group on Renal Transplantation

IV.11 Paediatrics (specific problems)

F. **Routine childhood vaccination** should be completed whenever possible prior to transplantation, in addition to vaccination against **hepatitis B** and **varicella**. **Anti-hepatitis A** and **anti-pneumococcal** vaccination are recommended. (Evidence level C)

Nephrol Dial Transplant 2002; 17: 55

AST Vaccination Recommendations

American Journal of Transplantation 2013; 13: 311–317
Wiley Periodicals Inc.

doi: 10.1111/ajt.12122

Special Article

Vaccination in Solid Organ Transplantation

L. Danziger-Isakov[a,*], D. Kumar[b] and the AST Infectious Diseases Community of Practice

Evidence Level

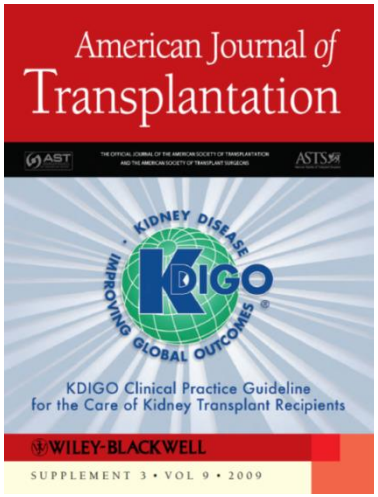
Grade of recommendation	
Level 1 „We recommend“	Most patients should receive the recommended course of action.
Level 2 “We suggest“	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and references.
Quality of evidence	
A	High quality of evidence
B	Moderate quality of evidence
C	Low quality of evidence
D	Very low quality of evidence

Am J Transplant 2009;9(S3):S1-155

Vaccination Recommendations for Paediatric RTx Patients

Vaccine	Before RTx	After RTx	Titre Control	Evidence Grade
Tetanus	+	+	+	1B
Diphtheria	+	+	-	B
Pertussis	+	+	-	C
HiB	+	+	+	1C
Poliovirus (IPV)	+	+	-	2B
Hepatitis B	+	+	+	1B
Pneumococcal	+	+	+	1B
Meningococcal	+	+	-	C
HPV	+	+	-	C
Influenza	+	+	-	1B
Hepatitis A	+	+	+	1B
Measles	+	-	+	1B
Mumps	+	-	+	1B
Rubella	+	-	+	1B
Varicella	+	-?	+	1B
Rotavirus	+	-	-	C
Rabies	*Exposure*	*Exposure*	-	*C*
BCG	*Exposure*	-	-	*C*

Am J Transplant 2013; 13: 311

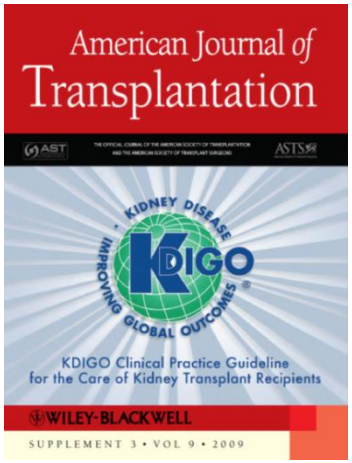


Am J Transplant 2009; 9(S3): 1-155

Vaccine	After RTx	Titre Control	Evidence Grade
Tetanus	+		1D
Diphtheria	+		1D
Pertussis	+		1D
HiB	+		1D
Hepatitis B	Titre <10 U/l Europe <100 U/l	6 - 12 weeks after vaccination, yearly after RTx	2D
Poliovirus (IPV)	+		1D
Influenza A und B	Yearly*		1D
Pneumococcus	Every 3 – 5 years?		2D
Hepatitis A, Meningococcus, Rabies, FSME, Japan. Encephalitis (inact.), Salmonella typhi (inact.)	*In case of increased risk*		2D
Measles	*In case of epidemia?*		2C
Mumps	-		2C
Rubella	-		2C
Varicella	-		2C
Poliovirus (OPV)	-		2C
Intranasal influenza	-		2C
Yellow Fever	-		2C
Japan. Encephalitis (Live vacc.)	-		2C
Salmonella typhi (Live vacc.)	-		2C

No vaccinations within first 6 months after RTx except

***Influenza - 1 month post-transplant at the earliest**



KDIGO

Research Recommendations

Studies are needed to determine:

- the optimal timing of immunization in KTRs;
- the durability of immunologic response in KTRs vaccinated before and after transplantation.

Am J Transplant 2009; 9(S3): 1-155

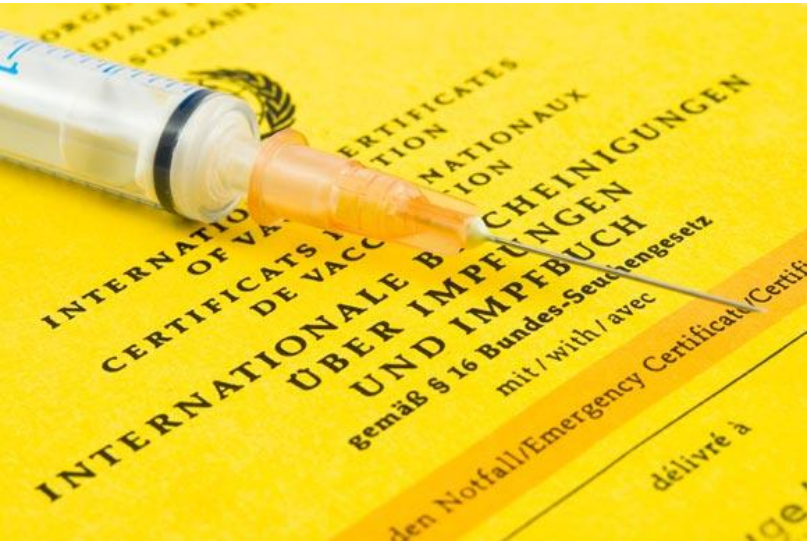
Vaccination and Immunisation Status in European Paediatric Renal Transplant Recipients: A CERTAIN Analysis

Aims

- Analysis of **vaccination status and vaccination titres** pre- and post-transplant and evaluation according to country-specific vaccination schedules and era
- Documentation of **a secondary antibody loss** after RTx and **the efficacy of re-vaccination**
- Analysis of the clinical efficacy of vaccinations, i.e. **the prevalence of vaccination-preventable diseases post-transplant**
- Determination of the impact of post-transplant vaccinations on **the development of HLA antibody levels** (in a subset of patients where data on HLA antibody levels are available)

Patient Cohort
(n = 254)

Age at RTx (yrs)	10.0 ± 5.6
Male gender	158 (62.2%)
Caucasian, n (%)	237 (93.3%)
Living donation, n (%)	98 (38.6%)
HLA mismatches	2.4 ± 1.3
Baseline eGFR (ml/min·1.73 m^2)*	80.5 ± 27.2



Vaccination Status Before RTx

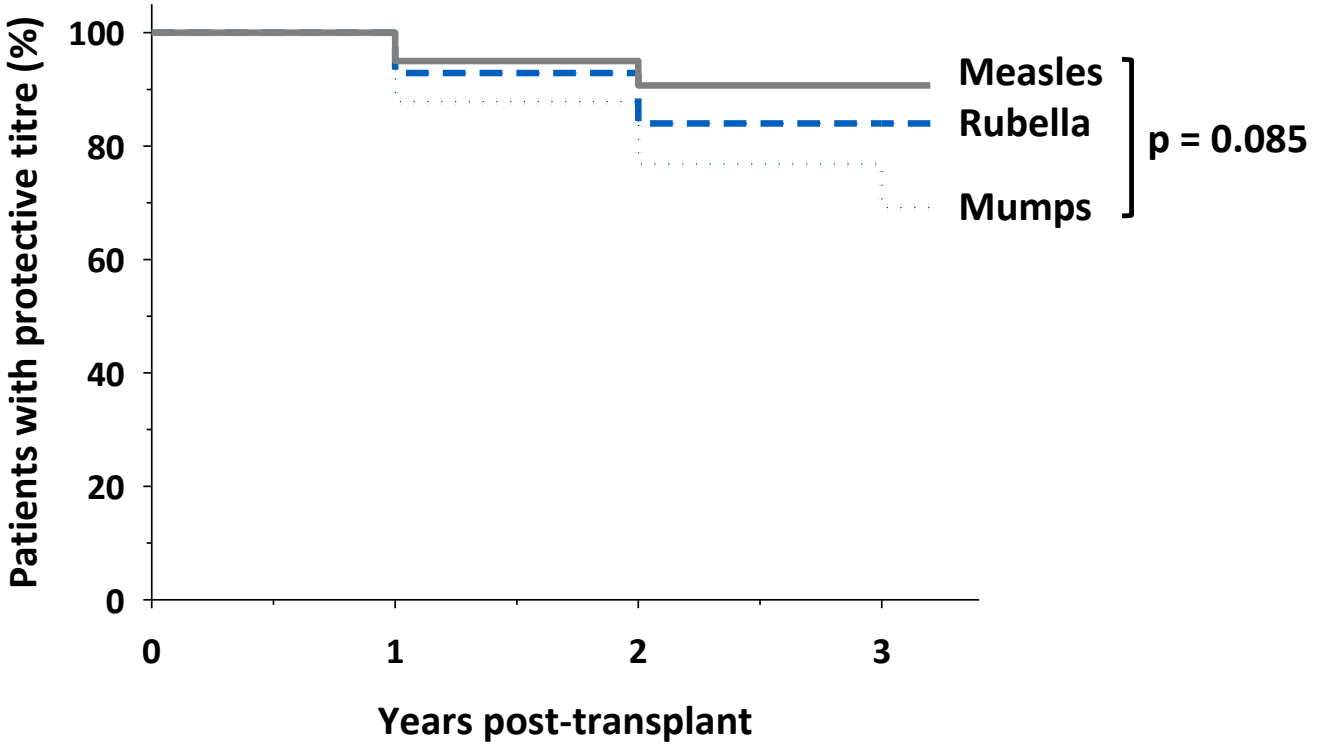
Summary 1

- Pretransplant, complete vaccination schedule for most vaccines in only 2/3 of patients
- Low vaccination rates against **HPV (27.3%), pneumococcal (42.2%)** and **meningococcal infections (47.9%)**
- Reduced rate of protective titres in uremic children prior to RTx, especially for **diphtheria (38.5%)** and **pertussis (21.3%)**
- Slightly higher rate of protective HBsAb titres in paediatric RTx candidates than in healthy children
- Recommended **HBsAb titre > 100 I.U./L in only 58.1% patients** before RTx
- Comparable rates of protective titres against MMR prior to RTx, but **two doses required, especially for mumps**

Vaccination Titres

Before and after RTx

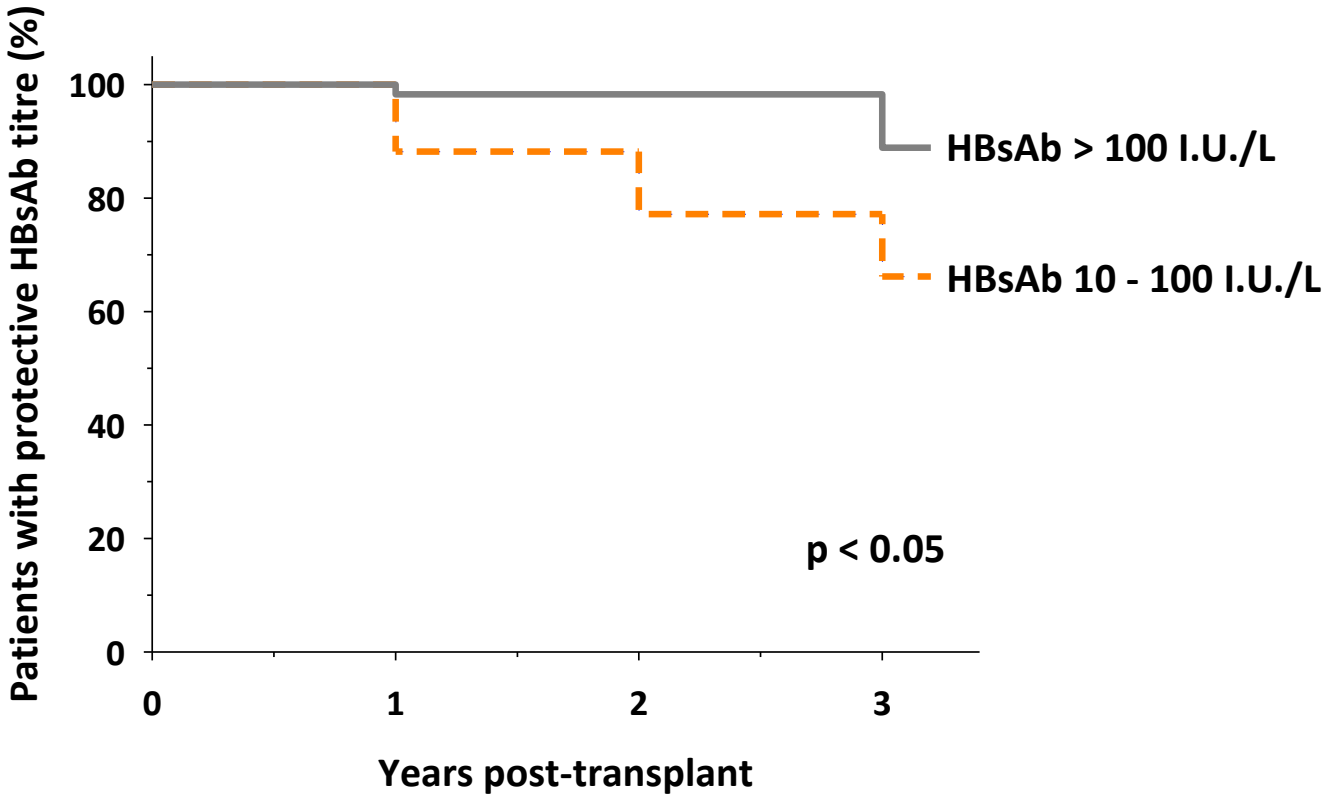
MMR Titres



Patients at risk:

Measles	**40**	**38**	**22**	**15**	**15**
Rubella	**42**	**39**	**21**	**14**	**14**
Mumps	**33**	**29**	**16**	**10**	**9**

Hepatitis B Titre



Patients at risk:

HBsAb > 100 I.U./L	58	57	30	21	19
HBsAb > 10 I.U./L	17	15	8	7	6

Summary 2

- **Secondary titre loss** post-transplant in 39.6% patients
  - **Live vaccines:** remarkable titre loss against **varicella** and **mumps** (no revaccinations with live vaccines recommended)
  - **Inactivated vaccines:** pronounced titre loss against **tetanus, diphtheria, hepatitis B, pneumococcal infection**
- Significantly lower HBsAb titre loss if pre-transplant **HBsAb titre > 100 I.U./L**
- Low revaccination rates (inactivated vaccines)
- Low protective titres against **pertussis (14.3%)** and **hepatitis B (37.5%)** after revaccination
- AST recommendation reasonable: post-transplant **titre measurement against tetanus, hepatitis B and pneumococcal infections**

Conclusion

- **Completion of the vaccination schedule** should be aimed at in all paediatric RTx candidates **before RTx**, particularly completion of live virus vaccinations, which are usually contraindicated after RTx.

- Post-transplant **measurement of vaccination titres**, including titres against tetanus, diphtheria, hepatitis B and pneumococcal infections, is reasonable to optimize the time point of **revaccinations** after RTx.

Heidelberg University Hospital

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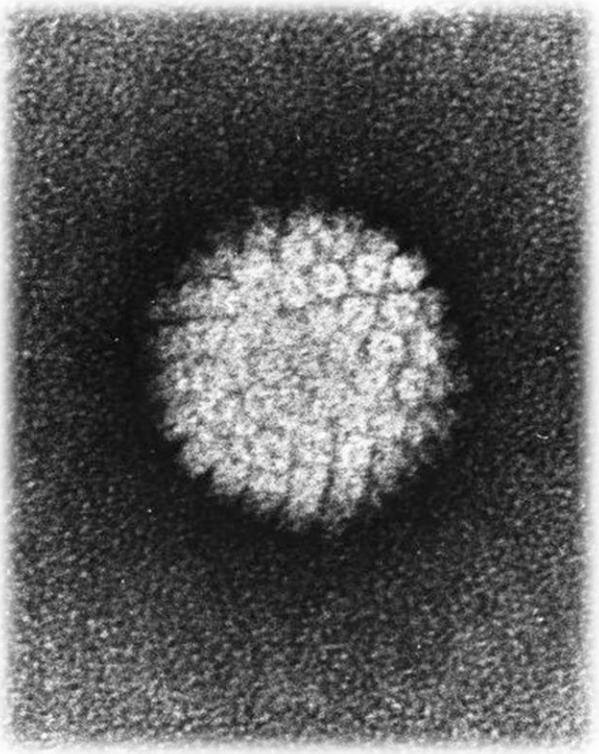
Immunogenicity of routine HPV vaccination in children pre- and post-transplant

A CERTAIN Study

Human papilloma virus (HPV) in immunocompromised patients

- Rapid progression of HPV infection → severe, persistent and extensive manifestations of HPV disease[1]
- High risk for HPV-related warts and skin cancers[2]
- **Risk** for HPV-related malignancies **post-transplant: 20-100x higher**



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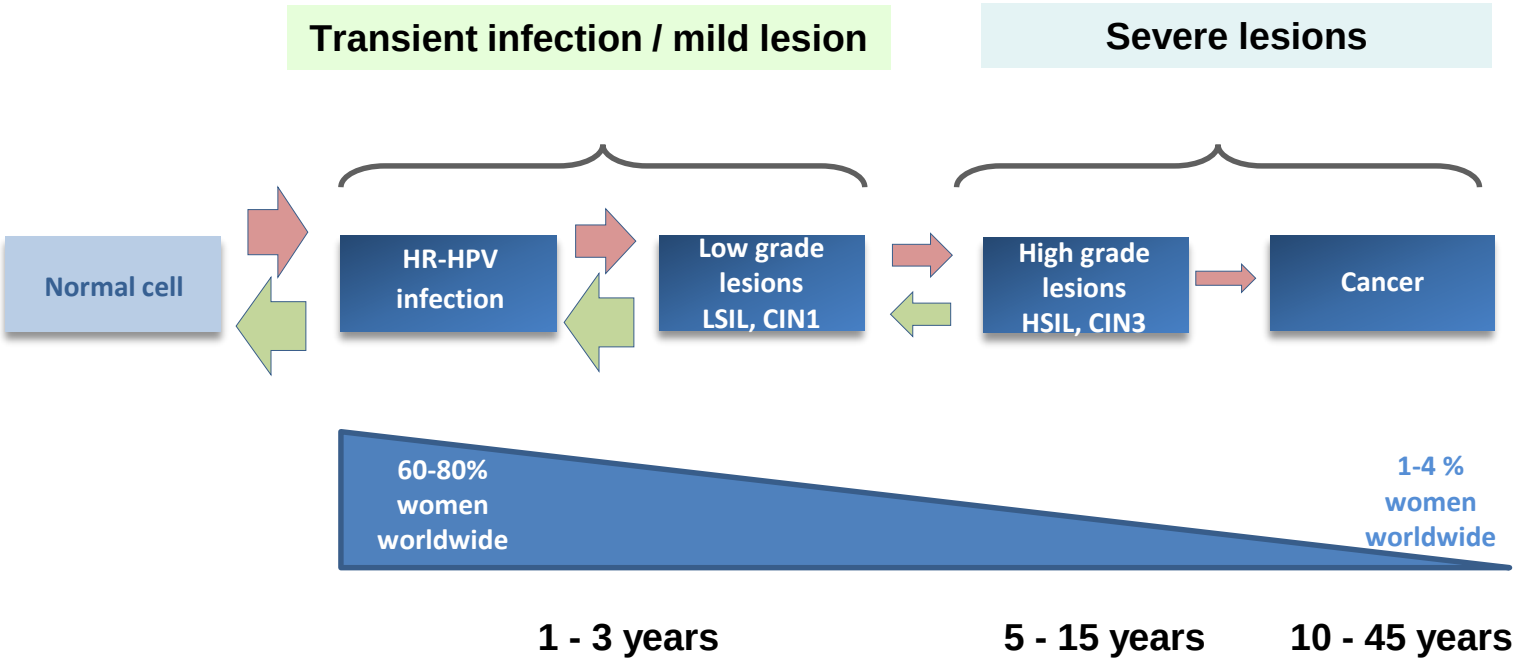
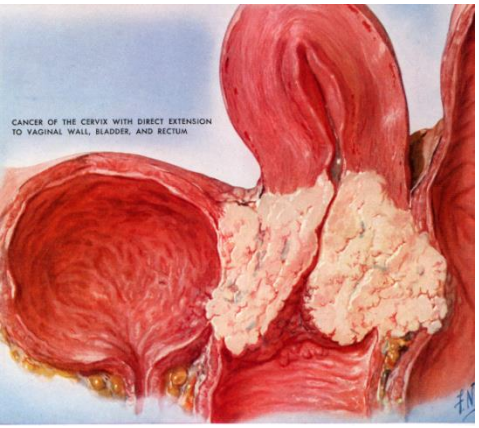
[1]Reusser et al. 2015, [2]Avery et al. 2008

Natural history of HPV infection and cervical lesion

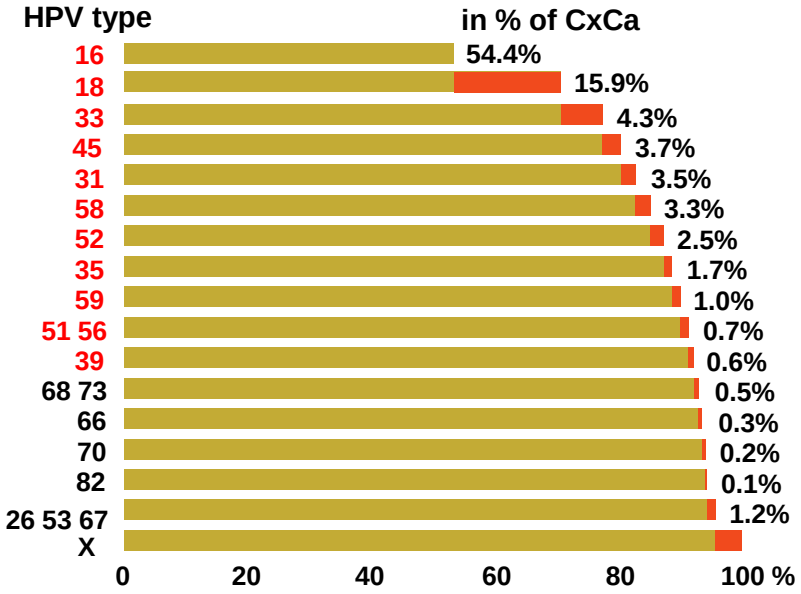


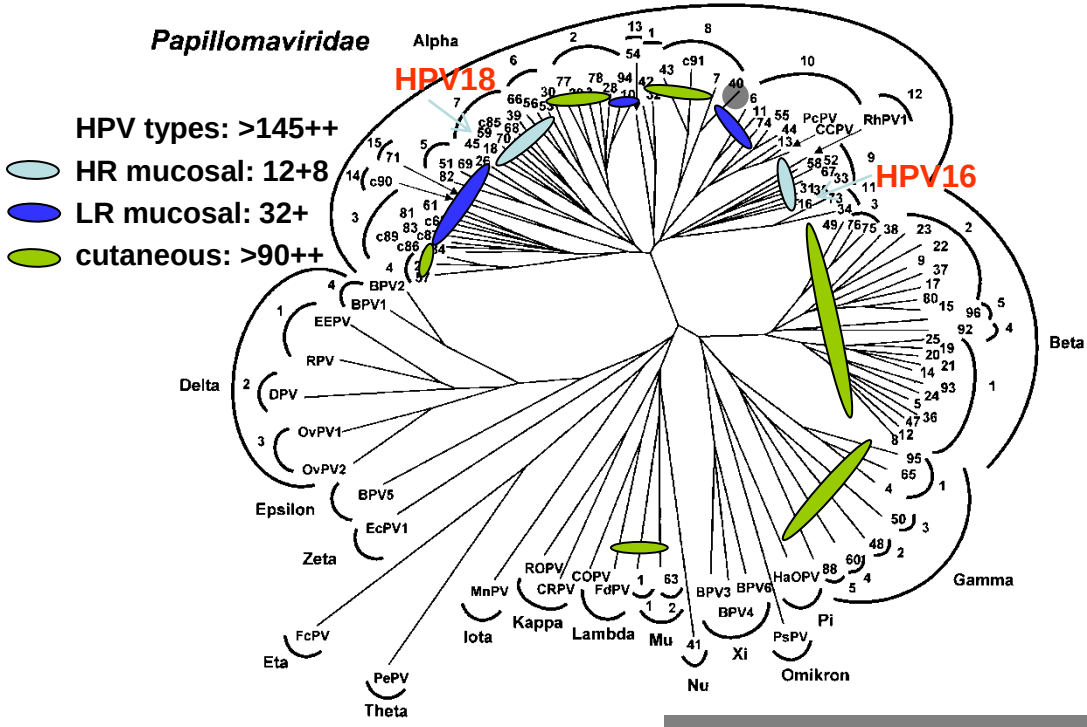
Cancer of the uterine cervix and Human papillomavirus, HPV



- **Persistent infection with one of 12 - 20 carcinogenic (HR-)HPV types is a necessary cause for development of CxCa**
- **Oncogenic HPV types differ in their carcinogenic risk: 16 > 18 > 31, 45, 33, 58 > others**
- **Secondary CxCa prevention is based on detection and removal of advanced cervical intraepithelial neoplasia (CIN3)**
- **In CxCa precursor screening the paradigm is currently changing from morphology (cytology) to virology (HPV testing)**

IARC Monograph 100B, WHO, 2010:
12 carcinogenic (class I) HPV types
8 probably/possibly carcinogenic (class IIa/b)





Modified from de Villiers et al., 2004

Cervical cancer in Europe

mortality
incidence

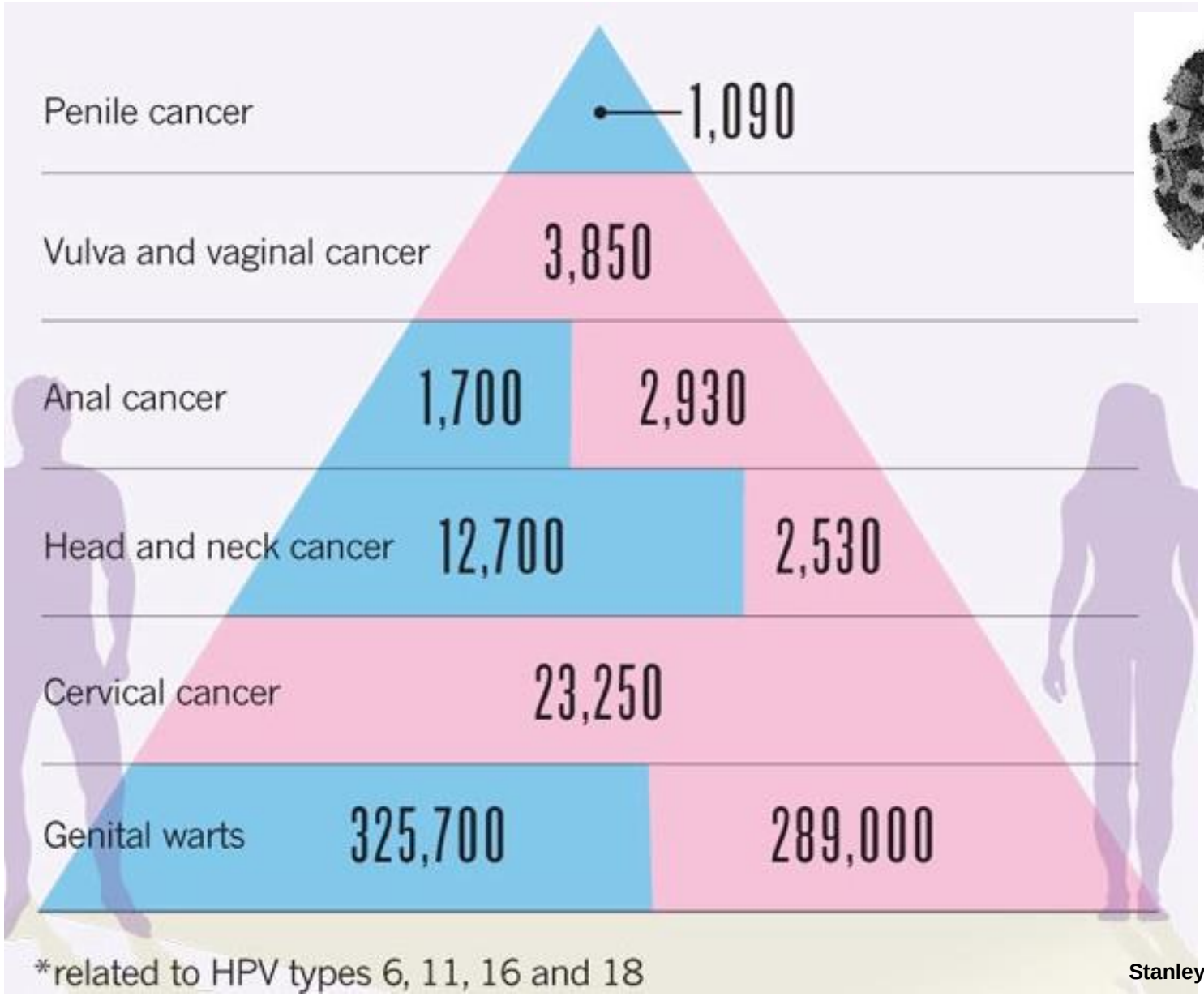
cases/100.000 women/year
age-standardized

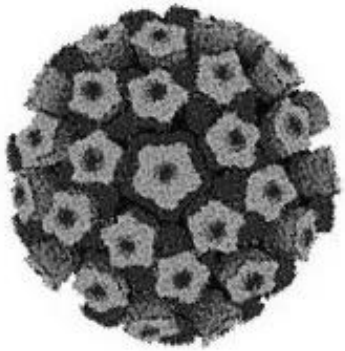
Figure 1: Cervical cancer rates across Europe

* The Former Yugoslav Republic of Macedonia.
** Data for Serbia and Montenegro taken from the period before separation.

Globocan 2002

Mucosal HPV-Induced Diseases by Gender
New Cases/Year, Europe





Stanley 2012 Nature 488:S10

HPV vaccination

Cervarix®

- HPV 16 & 18

→ 70% of cervical cancer[1]

GARDASIL®

- HPV 6, 11, 16 & 18

→ 90% of anogenital warts[1]

GARDASIL®9

- HPV 6, 11, 16, 18, 31, 33, 45, 52 &58

→ further 20% of cervical cancer[2]

[1]Kumar et al. 2013, [2]Brotherton et al. 2015

Vaccination Status before RTx - Inactivated Vaccines

Vaccine	Complete schedule	≥ 1 dose	No
Tetanus (n = 251)	177 (70.5%)	250 (99.6%)	1 (0.4%)
Diphtheria (n = 251)	177 (70.5%)	250 (99.6%)	1 (0.4%)
Pertussis (n = 248)	177 (71.3%)	233 (94.0%)	15 (6.1%)
Polio (n = 250)	202 (80.8%)	249 (99.6%)	1 (0.4%)
HiB (n = 239)	171 (71.5%)	215 (90.0%)	24 (10.0%)
Hepatitis B (n = 228)	202 (71.6%)	227 (99.6%)	1 (0.4%)
Pneumococcal (n = 173)	73 (42.2%)	105 (60.7%)	68 (39.3%)
Meningococcal (n = 169)	81 (47.9%)	87 (51.5%)	82 (48.5%)
HPV (n = 33)	9 (27.3%)	11 (33.3%)	22 (66.7%)

Data derived from CERTAIN registry study:
Höcker et al. (2015) "Vaccination and Immunisation Status in European Paediatric Renal Transplant Recipients"

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Aim and objectives

Aim:

- Prospective analysis of the response to **routine HPV vaccination** in paediatric patients with
  - **end-stage chronic kidney disease**
  - after **kidney** and/or **liver** Tx

Objectives:

- Comparison of **HPV titres** after vaccination
- Association of **secondary antibody loss** with immunosuppression (Tx) and uraemia (CKD)
- Comparison of different **vaccination schedules**

Study design

- **Multi-country & -centre** cohort study within CERTAIN network
- **Prospective** convenient sample collection of patients receiving **routine HPV vaccination**
- **Age-matched controls** derived from Indian HPV vaccination study data[1]

[1]Sankaranarayanan et al. 2015

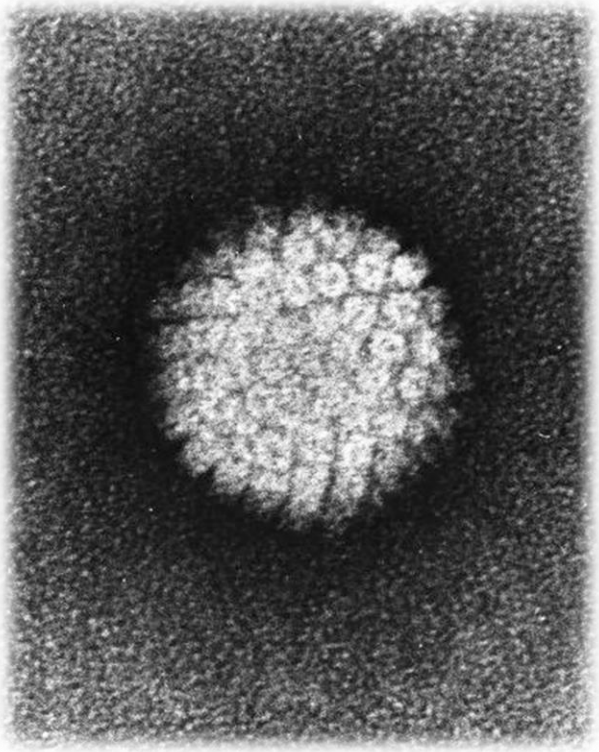
Laboratory analysis

DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

- German Cancer Research Centre Heidelberg
  Molecular diagnostics of oncogenic infections
  - High-throughput neutralization assay of natural and vaccine-induced antibodies

    → HPV titres
- Routine laboratory analysis at study sites to be included in CERTAIN registry

Immunogenicity of HPV vaccination in children pre & post-transplant?



Join the efforts!

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Conclusions I

- Transplant candidates and recipients are at increased risk of infectious complications of vaccine-preventable diseases.
- Every effort should be made to ensure that transplant candidates, **their household members** and **healthcare workers** have completed the full complement of recommended vaccinations prior to transplantation.
- Since the response to many vaccines is diminished in organ failure, transplant candidates should be immunized early in the course of their disease.

Conclusions II

- Live vaccines are usually contraindicated after transplantation.
- Post-transplant administration of varicella vaccine in pediatric transplant patients has been attempted in a research setting.
- Accumulating evidence in pediatric transplant recipients suggests that varicella vaccine is safe and immunogenic after transplantation
- However, these studies are relatively small in size. In light of these studies, it is recommended that at this time, vaccination should be performed only in a carefully controlled setting.

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International Pediatric Transplant Association

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German Vaccination Schedule

VACCINATION SCHEDULE

Sprache: **Englisch**

Vaccinations should be administered at the earliest possible age.
An assessment of vaccination status is recommended at all ages.
Any missed vaccinations should be administered immediately, in accordance with the recommendations for the relevant age group.

German Standing Committee on Vaccination (STIKO) recommendations, 2014.
www.stiko.de

ROBERT KOCH INSTITUT

VACCINATION \ AGE	(in weeks) 6	Infants 2	Infants 3 (U4)	(in months) 4	Toddlers 11–14 (U6)	Toddlers 15–23 (U7)	Children 2–4 (U7A/8)	Children 5–6 (U9)	(in years) 7–8 (U10)	Adolescents 9–14 (J1)	Adolescents 15–17	Adults from 18	Adults from 60
Tetanus		G1	G2	G3	G4	N		A1	N	A2		A (every 10 years, f) N if required	
Diphtheria		G1	G2	G3	G4	N		A1	N	A2		A (every 10 years, f) N if required	
Whooping cough Pertussis		G1	G2	G3	G4	N		A1	N	A2		A (N if required) f	
Polio Poliomyelitis		G1	G2 a	G3	G4	N				A1		N (if required)	
Hepatitis B		G1	G2 a	G3	G4	N							
Hib *Haemophilus influenzae type b*		G1	G2 a	G3	G4	N							
Pneumococcal disease		G1	G2	G3	G4	N						S c	
Rotaviruses	G1 b	G2	(G3)										
Meningococcal disease Serogroup C					G1 (from 12 months)		N						
Measles					G1	G2	N					S d	
Mumps Rubella					G1	G2	N						
Chicken pox Varicella					G1	G2	N						
Flu Influenza												S (annually)	
HPV Human papillomaviruses										G1 e	G2 e	N e	

Dates of next vaccinations

Gefördert durch:
Bundesministerium für Gesundheit
aufgrund eines Beschlusses des Deutschen Bundestages

EXPLANATORY NOTES

- **G** **PRIMARY IMMUNISATION** (up to 4 doses of vaccine G1–G4)
- **S** **STANDARD VACCINATION**
- **A** **BOOSTER VACCINATION**
- **N** **CATCH-UP VACCINATION** (primary immunisation of persons not yet vaccinated or completion of an incomplete vaccination series)
- **U** **Well-child visit**
- **J** **Well-adolescent visit** (J1 aged 12–14 years)

a This dose is not required if a monovalent vaccine is administered.
b The 1st vaccine dose should be administered from the age of 6 weeks. Depending on the type of vaccine, 2 or 3 doses are required at intervals of a minimum of 4 weeks.
c Single dose vaccination with polysaccharide vaccine, booster vaccination only recommended for specific indications.
d Single dose vaccination for all individuals ≥ 18 years with unclear vaccination status and who were born after 1970, who have not been vaccinated or only received one vaccination as a child. Preferably with an MMR vaccine.
e Standard vaccination for girls aged 9-13 or 9-14 years (depending on the vaccine used), for number of vaccine doses see specialised information!
f Td booster vaccination every 10 years. The next Td vaccination that is due is to be administered as a single dose vaccination in the form of Tdap or, if indicated, in the form of a Tdap-IPV combination vaccination.