Aus dem Robert Koch-Institut,

Abteilung für Infektionsepidemiologie

DISSERTATION

Seroepidemiologie und bevölkerungsbezogene Infektions- und Erkrankungsrisiken von Humanen Papillomviren (HPV) und Zytomegalievirus (CMV) anhand von Seren der zwei repräsentativen Gesundheitssurveys 'Kinder- und Jugendgesundheitssurvey (KiGGS-Basiserhebung)' und 'Survey zur Gesundheit von Erwachsenen (BGS98)'

zur Erlangung des akademischen Grades

Doctor rerum medicinalium (Dr. rer. medic.)

vorgelegt der Medizinischen Fakultät

Charité – Universitätsmedizin Berlin

von

Anna Dorothea Loenenbach

aus Neustadt an der Weinstraße

Datum der Promotion: 25. Juni 2023

1 INHALTSVERZEICHNIS

Abkürzungsverzeichnis II
1. Zusammenfassung der Publikationspromotion 1
1.1. Abstract 1
1.1.1. Abstract Deutsch 1
1.1.2. Abstract Englisch 2
1.2. Einleitung 4
1.3. Material und Methodik 7
1.4. Ergebnisse 11
1.4.1. HPV-Seroprävalenzen und Risikofaktoren bei Erwachsenen 12
1.4.2. HPV-Seroprävalenzen und Risikofaktoren bei Kindern und Jugendlichen 13
1.4.3. CMV-Seroprävalenz und Risikofaktoren bei Erwachsenen 15
1.5. Diskussion 15
1.5.1. HPV-Seroepidemiologie bei Erwachsenen, Kindern und Jugendlichen 15
1.5.2. CMV-Seroepidemiologie bei Erwachsenen 18
1.5.3. Stärken und Limitationen 19
1.5.4. Zusammenfassung und Ausblick 21
1.6. Literaturverzeichnis 24
2. Eidesstattliche Versicherung 28
3. Anteilserklärung an den erfolgten Publikationen 29
5. Originalarbeiten als Promotionsleistung 31
5.1. Publikation 1 31
5.2. Publikation 2 45
5.3. Publikation 3 66
6. Lebenslauf 93
7. Publikationsliste 95
8. Danksagung 100

ABKÜRZUNGSVERZEICHNIS

BGS98	Bundes-Gesundheitssurvey 1998
CMV	Zytomegalievirus
DEGS1	Studie zur Gesundheit Erwachsener in Deutschland
DKFZ	Deutsches Krebsforschungszentrum, Heidelberg
DNA	Desoxyribonukleinsäure
GST	Glutathion-S-Transferase
HPV	Humane Papillomviren
HPV-kut	Kutane HPV-Typen in der Studie:1, 4, 8, 10, 38, 41, 49
HPV-muk	Mukosale HPV-Typen in der Studie: 6, 11, 16, 18, 31, 33, 35, 39, 45, 52, 58, 59
HR-Typen	HPV Hochrisikotypen in der Studie: 16, 18, 31, 33, 35, 39, 45, 52, 58, 59
IARC	Internationale Agentur für Krebsforschung
IfSG	Infektionsschutzgesetz
KI	Konfidenzintervall
KiGGS	Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland
LR-Typen	HPV Niedrigrisikotypen: 6, 11
MFI	Mittlere Fluoreszenzintensität
PR	Prevalence Ratios
RKI	Robert Koch-Institut
RRP	Rezidivierende respiratorische Papillomatose
SES	Sozioökonomischer Status
STI	Sexuell übertragbare Infektionen

1. ZUSAMMENFASSUNG DER PUBLIKATIONSPROMOTION

1.1. ABSTRACT

1.1.1. ABSTRACT DEUTSCH

HINTERGRUND

Die beiden Surveys ‚Bundes-Gesundheitssurvey 1998' (BGS98) für die erwachsene Bevölkerung sowie ‚Gesundheit von Kindern und Jugendlichen in Deutschland' (KiGGS-Basiserhebung, 2003–2006) waren die ersten repräsentativen Gesundheitssurveys für das wiedervereinigte Deutschland. Die Surveys umfassten unter anderem Interviews, medizinische Untersuchungen und Blutprobenabnahmen. Bisher waren keine repräsentativen serologischen Daten zur Verbreitung von Humanen Papillomviren (HPV) und Zytomegalievirus (CMV) vorhanden. Ziel der vorliegenden Arbeit war es, die aus diesen zwei Gesundheitssurveys noch verfügbaren Blutproben zu nutzen und auf Antikörper gegen verschiedene HPV-Typen sowie auf CMV-Antikörper zu testen. Über die Ermittlung der Seropositivität als Proxy einer bisherigen kumulativen Exposition gegenüber dem jeweiligen Erreger sollten darauf aufbauend Seroprävalenzen berechnet und Risikofaktoren identifiziert werden.

METHODEN

Die vorhandenen Rückstellproben wurden am Deutschen Krebsforschungszentrum mittels eines eigens entwickelten Multiplex-Assays auf verschiedene HPV- und auf CMV-Antikörper (nur BGS98-Proben) getestet. Darüber hinaus wurde auch auf weitere sexuell übertragbare Infektionserreger (STI; *Mycoplasma genitalium*, Herpes simplex Virus 2, und *Chlamydia trachomatis)* getestet. Die 19 HPV-Typen umfassten verschiedene kutane, mukosale und für die Karzinomentwicklung verantwortliche Hochrisikotypen (HPV-HR). Hieraus wurden Geschlechts- und Alters-stratifizierte Seroprävalenzen berechnet und mittels Regressionsanalysen Risikofaktoren von HPV- und CMV-Seropositivität ermittelt.

ERGEBNISSE

Von 18.774 getesteten Proben wiesen 6,7% (95%-Konfidenzintervall (KI): 6,0–7,4) der Erwachsenen und 2,6% (95%-KI: 2,2–3,0) der Kinder und Jugendlichen Antikörper gegen HPV-HR-Typ 16 auf. Insgesamt 28% (95%-KI: 26–29) der Erwachsenen und 13% (95%-KI: 12–14) der Kinder und Jugendlichen waren positiv für mindestens einen der

zehn getesteten HPV-HR-Typen. Seroprävalenzen kutaner HPV-Typen variierten bei Erwachsenen zwischen 8,7% (95%-KI: 7,8–9,6; HPV-41) und 35% (95%-KI: 33–36; HPV-4) und bei Kindern und Jugendlichen zwischen 4,0% (95%-KI: 3,6–4,4; HPV-38) und 32% (95%-KI: 31–33; HPV-1). Bei den Regressionsanalysen waren Seropositivität auf andere STIs und Anzahl bisheriger Sexualpartner*innen die stärksten unabhängigen Prädikatoren einer HPV-16-Seropositivität bei Erwachsenen, bei Kinder und Jugendlichen das Alter.

Die CMV-Seroprävalenz der Erwachsenen betrug 57% (95%-KI: 55–59); 48% der Frauen im gebärfähigen Alter waren CMV-seronegativ. Unabhängige Prädikatoren einer CMV-Seropositivität (für Männer und Frauen) waren Alter, Geburtsland, Rauchen, Wohnregion, Anzahl von <18-jährigen Haushaltsmitgliedern und Bildungsstatus.

DISKUSSION

Auf Grundlage der beiden Bevölkerungssurveys konnten erstmalig repräsentative HPV bzw. CMV-Seroprävalenzen für Erwachsene und insbesondere für Kinder und Jugendliche geschätzt werden, welche als Proxys einer bisherigen kumulativen Exposition mit dem jeweiligen Erreger interpretiert werden können. Durch die Analyse der geschlechts- und altersspezifischen Seroprävalenzen sowie entsprechender Risikofaktoren können die Ergebnisse den Kenntnisstand zur Verbreitung und Bedeutung von HPV und CMV erweitern und helfen, bestehende sowie zukünftige Präventionsmaßnahmen zu evaluieren und anzupassen.

1.1.2. ABSTRACT ENGLISCH

BACKGROUND

The 'German National Health Interview and Examination Survey 1998 (GNHIES98)' for the adult population and the 'German Health Interview and Examination Survey for Children and Adolescents (KiGGS, 2003–2006)' were the first representative health surveys for Germany after the German reunification. The aim of the present study was to use the already collected blood samples for testing for HPV and CMV antibodies. By determining seropositivity as a proxy of previous cumulative exposure to the respective pathogens, seroprevalences could be calculated and risk factors identified.

METHODS

The samples were tested for 19 different HPV type antibodies and CMV antibodies (BGS98 samples only) at the German Cancer Research Centre using an in-house developed multiplex assay. Furthermore, it was tested for antibodies against other sexually transmitted infections (STI; including *Mycoplasma genitalium*, Herpes simplex virus type 2 and *Chlamydia trachomatis*). HPV types included cutaneous, mucosal and, as causative agents of diverse carcinoma development identified high risk (HPV-HR) types. Gender- and age-stratified seroprevalences were calculated and regression analyses used to determine risk factors of HPV and CMV seropositivity.

RESULTS

18,774 samples of both surveys were tested. Seropositivity for HPV-HR-16 was 6.7% (95% confidence interval (CI): 6.0–7.4) for adults and 2.6% (95%CI: 2.2–3.0) for children and adolescents. Overall 28% (95%CI: 26–29) of adults and 13% (95%CI: 12–14) of children and adolescents were seropositive for at least one of the HPV-HR types. Seroprevalence of cutaneous HPV types varied in adults between 8.7% (95%CI: 7.8–9.6; HPV-41) and 35% (95%CI: 33–36; HPV-4) and in children and adolescents between 4.0% (95%CI: 3,6–4,4; HPV-38) and 32% (95%CI: 31–33; HPV-1). In the regression analyses, seropositivity for other STI and the number of previous sexual partners were the strongest non-dependent predictors of HPV-16 seropositivity in adults, as well as age in children.

CMV seroprevalence of adults was 57% (95%CI: 55–59). Overall 48% of women of childbearing age were still seronegative.

DISCUSSION

Seropositivity is a useful proxy for measuring previous cumulative HPV or CMV exposure. Based on two population-based health surveys, representative HPV and CMV seroprevalences for adults and especially for children and adolescents living in Germany could be estimated for the first time. By analysing gender- and age-specific seroprevalences and corresponding risk factors, the results can expand the knowledge on the spread of HPV and CMV in the German population and therefore, help to evaluate and adapt existing and future prevention measures.

1.2. EINLEITUNG

Die vorliegende Arbeit beruht auf der Nutzung von Daten und Blutproben der beiden Studien „Bundes-Gesundheitssurvey 1998“ (BGS98) sowie „Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland“ (KiGGS). Die beiden Bevölkerungssurveys wurden, neben weiteren epidemiologischen Gesundheitsstudien, im Auftrag des Bundesgesundheitsministeriums durchgeführt und sind Teil des Gesundheitsmonitorings des Robert Koch-Instituts (RKI). Sie entsprechen einer für die deutsche Wohnbevölkerung repräsentativen gesundheitlichen Momentaufnahme der Erwachsenen (BGS98) zum Ende der 1990er sowie der Kinder und Jugendlichen (KiGGS-Basiserhebung, im Folgenden KiGGS) zu Beginn der 2000er in Deutschland. Die BGS98-Studie war somit die erste repräsentative Untersuchung zum Gesundheitszustand der Erwachsenenbevölkerung in Deutschland nach der Wiedervereinigung (1, 2). Mit den KiGGS-Daten lagen für Deutschland erstmals umfassende und repräsentative Gesundheitsdaten für Kinder und Jugendliche vor (3).

Aus beiden Gesundheitssurveys standen von den damals gewonnenen Serumproben sogenannte Rückstellproben zur Verfügung, die im Rahmen der hier vorliegenden Promotionsarbeit für spezielle serologische Untersuchungen und zur Verknüpfung mit den damals erhobenen Surveydaten genutzt werden konnten. Dazu sollten die verfügbaren Proben vom RKI an das Deutsche Krebsforschungszentrum (DKFZ) in Heidelberg geschickt und dort mittels eines eigens entwickelten Multiplex Serologie-Verfahrens simultan auf Antikörper verschiedener zuvor festgelegter Erreger untersucht werden. Fokus der vorliegenden Arbeit waren die Antikörpernachweise von Humanen Papillomviren (HPV) und Zytomegalievirus (CMV).

CHARAKTERISTIKA UND KRANKHEITSLAST HUMANER PAPILLOMVIREN

HPV-Infektionen zählen zu den häufigsten sexuell übertragbaren Infektionen (sexually transmitted infection; STI) weltweit. HPV gehört zu der vielseitigen Papillomaviridae Virusfamilie und umfasst mittlerweile über 200 bekannte Typen. Diese werden nach unterschiedlichen Parametern unterteilt: HPV-Typen werden einerseits auf Grundlage ihrer phylogenetischen Beziehung in verschiedene Gattungen und Spezies eingeteilt (4). Diese umfassen drei Hauptgattungen: Alphapapillomavirus, Betapapillomavirus und Gammapapillomavirus. Weiterhin werden HPV-Typen in unterschiedliche Tropismen eingeteilt: 1) kutane HPV-Typen, welche Epithelzellen der Haut infizieren und 2)

mukosale HPV-Typen, welche Epithelzellen verschiedener Schleimhäute infizieren können. Ein drittes Einteilungsschema bezieht sich auf die potentiellen Krankheitsfolgen einer HPV-Infektion, insbesondere die Karzinogenität. Diese bezieht sich auf ihre Rolle als Verursacher verschiedener präkanzeröser Läsionen und Karzinome (5). Obgleich es eine Vielzahl an unterschiedlichen HPV-Typen gibt, besitzt jedoch nur ein kleiner Anteil karzinogene Eigenschaften, welche entsprechend, wie beispielsweise HPV-16 und HPV-18, als Hochrisikotypen (HR-Typen) bezeichnet werden.

Die Mehrheit der HPV-Infizierten entwickelt keine Symptome, und die Infektion verläuft transient und ist innerhalb der folgenden 12–24 Monate nicht mehr nachweisbar (6). Wenn HPV-Infektionen mit mukosalen HR-Typen persistieren, steigt jedoch das Risiko einer Folgeerkrankung, bzw. der Entwicklung oropharyngealer oder anogenitaler Karzinome (5, 6). Es existieren aber auch weitere klinische Manifestationen einer HPV-Infektion. Sogenannte Niedrig-Risiko (Low risk, LR) Typen, wie beispielsweise HPV-6 oder HPV-11, können zu externen, meist im Anogenitalbereich vorkommenden, gutartigen Warzen führen, die nicht nur bei Erwachsenen sondern auch bei Kindern diagnostiziert werden (7). Eine weitere, jedoch selten vorkommende, durch LR-HPV-Typen ausgelöste Erkrankung ist die rezidivierende respiratorische Papillomatose (RRP), welche zu einem Auftreten zumeist gutartiger Plattenepithelpapillomen im Bereich Kehlkopf, Luftröhre und Lunge führen kann. Demgegenüber stehen kutane HPV-Typen, wie beispielsweise HPV-1 oder HPV-4. Kutane HPV-Typen lassen sich sowohl auf gesunder Haut finden, als auch in Hautläsionen, welche sich beispielsweise als typische Hautwarzen an Füssen und Händen manifestieren (5). Überdies wird vermutet, dass auch bestimmte kutane Hauttypen in die Entstehung von Hautkrebs involviert sein können (8).

Seit 2007 sind in Deutschland Impfstoffe zur Prävention der Infektionen mit bestimmten HPV-Typen von der Ständigen Impfkommission (STIKO) empfohlen. Die HPV-Impfempfehlung wurde im Jahr 2018 von der bisherigen Beschränkung auf Mädchen auch auf Jungen im Alter von 9–14 Jahren ausgeweitet. Aktuell sind folgende Impfstoffe in Deutschland verfügbar: der bivalente HPV-Impfstoff Cervarix® (gegen die HPV-Typen: 16 und 18) und der nanovalente Impfstoff Gardasil®9 (gegen die HPV-Typen: 6, 11, 16, 18, 31, 33, 45, 52 und 58).

Die Erhebung von HPV-Antikörpern im Rahmen von Seroprävalenzdaten kann als Maß lebenslanger kumulativer HPV-Exposition zu einem Überblick über die Verbreitung, aber auch über potentielle Risikofaktoren von HPV beitragen. Gleichzeitig können

Seroprävalenzdaten im Vergleich vor und nach einer Impfeinführung zu einer Evaluation jeweiliger Impfstrategien eingesetzt werden. In Deutschland gab es bisher jedoch keine für die deutsche Bevölkerung repräsentativen Daten zur Seroepidemiologie von HPV, weder bei Erwachsenen noch bei Kindern und Jugendlichen; Studien zur letztgenannten Altersgruppe sind auch international rar (7, 9).

CHARAKTERISTIKA UND KRANKHEITSLAST DES ZYTOMEGALIEVIRUS

Das Zytomegalievirus gehört zur Familie der Herpesviridae und ist weltweit verbreitet. Die CMV-Seroprävalenz in der Allgemeinbevölkerung wird weltweit auf 45–100% geschätzt (10). Repräsentative CMV-Seroprävalenzen für die Bevölkerung in Deutschland lagen bisher noch nicht vor. Einzelne Studien ergaben eine CMV-Seroprävalenz bei Blutspendern von 38% bzw. etwa 47% bei Schwangeren (11-13).

Nach einer Erstinfektion mit dem Virus bleibt die Infektion latent. Typische Übertragungswege sind der Kontakt (als Tröpfchen- oder Schmierinfektion) mit CMV-kontaminierten Körperflüssigkeiten, wie Speichel, Urin, Spermasekreten sowie bei der Bluttransfusion. In immunkompetenten Personen verläuft eine CMV-Infektion zumeist asymptomatisch, während es bei immunsupprimierten Personen zu lebensbedrohlichen Komplikationen führen kann (14). CMV gilt mittlerweile als häufigster viraler Erreger einer kongenitalen Infektion (14). Bei Kindern kann eine kongenital erworbene CMV-Infektion zu schwerwiegenden neurologischen Schädigungen führen (15).

Bislang steht kein Impfstoff gegen CMV-Infektionen zur Verfügung, obgleich verschiedenen Hersteller seit einigen Jahren daran forschen. Eine weitere Herausforderung besteht in der fehlenden Wahrnehmung innerhalb der Bevölkerung über die Verbreitung und Tragweite von (kongenitalen) CMV-Infektionen, vor allem unter Schwangeren bzw. Frauen mit Kinderwunsch (16). Äquivalent zu HPV, kann auch die CMV-Seroprävalenz im Rahmen der Messung von CMV-Antikörpern als Marker einer bisherigen CMV-Exposition einen Beitrag zum Wissenstand der CMV-Verbreitung leisten. Im Vergleich zu anderen Ländern gab es bisher jedoch auch für CMV keine (repräsentativen) Daten zur Seroprävalenz in der Bevölkerung in Deutschland.

ZIELE UND FRAGESTELLUNGEN DER STUDIE

Das zugrundeliegende Ziel der vorliegenden Studien war es, die bereits vorhandenen Serumproben der zwei zuvor beschrieben Bevölkerungssurveys zu nutzen, um für die Bevölkerung in Deutschland repräsentative Daten zur Krankheitslast von HPV und CMV zum Zeitpunkt der Serumsprobenabnahme zu generieren.

Das primäre Studienziel war die serologische Erhebung von Antikörpern gegenüber verschiedenen HPV-Typen als Proxy einer bisher durchgemachten Infektion bei den Teilnehmenden (17, 18). Die Auswahl der beiden (älteren) Studien begründet sich mit dem jeweiligen Erhebungszeitraum, der für HPV besonders relevant ist, da er noch vor der Einführung der HPV-Impfung lag. Somit können mit Hilfe der Daten seroepidemiologische Fragestellungen in Bezug auf HPV bei der deutschen Bevölkerung in der Präimpfära beantwortet werden. Diese können in Zukunft mit Daten aus der Impfära verglichen und somit als Grundlage für eine Evaluation der HPV-Impfeinführung verwendet werden. Für die hier vorliegende Arbeit wurden folgende Hauptfragen definiert:

- Wie hoch ist die Prävalenz von Antikörpern gegen verschiedene HPV-Typen in der deutschen Bevölkerung? Gibt es einen Geschlechts-Unterschied der HPV-Seroprävalenzen? Gibt es einen Alters-Unterschied der HPV-Seroprävalenzen?
- Welche soziodemographischen und verhaltensbasierten Faktoren sind mit einer HPV-Seropositivität assoziiert?

Ein weiteres Ziel der Studie war es, die vorhandenen Rückstellproben auf CMV zu testen (19), da bisher keine bevölkerungsbezogenen CMV-spezifischen Ig-Seroprävalenzdaten für Deutschland verfügbar waren. Der serologischen Untersuchung von CMV lagen folgende Fragestellungen zugrunde:

- Wie hoch ist die Prävalenz von CMV-Antikörpern in der deutschen Bevölkerung? Gibt es einen Geschlechts-Unterschied der CMV-Seroprävalenz? Gibt es einen Alters-Unterschied der CMV-Seroprävalenz?
- Welche soziodemographischen und verhaltensbasierten Faktoren sind mit einer CMV-Seropositivität assoziiert?

1.3. Material und Methodik

Studienpopulationen

Die Studienpopulationen basieren auf zwei Langzeitstudien des RKI zur Gesundheit von Erwachsenen (BGS98) sowie von Kindern und Jugendlichen (KIGGS) in Deutschland. Der Erwachsenengesundheitssurvey BGS98 wurde im Erhebungszeitraum 1997–1999 durchgeführt (1, 2). Insgesamt nahmen an dem Survey 7.124 Personen zwischen 18 und 79 Jahren aus 120 Städten und Gemeinden aus allen Bundesländern in

Deutschland teil. Somit stellt BGS98 die erste repräsentative Studie zum Gesundheitszustand der Erwachsenenbevölkerung im wiedervereinigten Deutschland dar.

Von 2003 bis 2006 fand die Basiserhebung von KiGGS mit insgesamt 17.641 Studienteilnehmenden im Alter von 0–17 Jahre statt (3). Danach erfolgten noch zwei weitere Erhebungswellen (2009–2012 und 2014–2017). Inhalt der jeweiligen Erhebungen sind die altersabhängigen Befragungen von Eltern und Kindern bzw. Jugendlichen. Neben den Befragungen kommen in bestimmten Abständen auch medizinische Untersuchungen und Laboranalysen hinzu. Bei KiGGS handelt es sich zudem um eine Langzeit-Kohorte, da ein Teil der Kinder und Jugendlichen aus der Basiserhebung bis zum Alter von 18 Jahren in den Folgeerhebungen wiederholt untersucht wurden.

DATENSCHUTZ

Die BGS98-Studie wurde nach Vorabprüfung des Bundes- und Landesbeauftragten für den Datenschutz nach den entsprechenden allgemeinen Richtlinien durchgeführt. Da es zum aktuellen Zeitpunkt der Durchführung der BGS98-Studie keine Regularien bezüglich zuständigen Ethikkommissionen gab, liegt für BGS98 kein Ethikvotum vor. Allerdings wurde ein positives Votum der Ethikkommission der Charité-Universitätsmedizin Berlin (Nr. EA2/047/08) für die Folgestudie DEGS1 eingeholt. Alle Teilnehmenden von BGS98 unterzeichneten eine schriftliche Teilnahme-Einwilligungserklärung.

Die KiGGS Studie wurde ebenfalls nach den Richtlinien der Bundes- und Landesbeauftragten für den Datenschutz durchgeführt und zusätzlich von der Ethikkommission der Charité Universitätsmedizin Berlin und dem Bundesbeauftragten für Datenschutz genehmigt. Sie orientierte sich durch Kontrollen zur internen und externen Qualitätssicherung während der Studie zudem an den Leitlinien zur Sicherung „Guter Epidemiologischer Praxis“ der Deutschen Gesellschaft für Epidemiologie. Die Eltern/Erziehungsberechtigten stimmten für ihr minderjähriges Kind der Teilnahme an KiGGS (Befragung und Untersuchung) schriftlich zu. Die Durchführung und Auswertung der gesamten Studie wurde von einem wissenschaftlichen und ethischen Beirat überwacht und begleitet.

SURVEY METHODEN: SAMPLING, GEWICHTUNG UND VARIABLENAUSWAHL

Der BGS98 hatte zum Ziel, repräsentative Aussagen zum Gesundheitszustand der deutschen Wohnbevölkerung im Alter von 18–79 Jahren in den Jahren 1997–1999 zu treffen. Die 120 Untersuchungsorte (sample points) wurden in einer mehrfach geschichteten zweistufigen Zufallsstichprobe ausgewählt. Die erste Stufe der Zufallsstichprobenziehung umfasste die zufallsbasierte Auswahl von Gemeinden, geschichtet nach

Bundesland, Regierungsbezirk und Gemeindegrößenklasse (BIK-Gemeindetyp). Dabei wurde eine disproportionale Verteilung der west- und ostdeutschen Bundesländer entsprechend der Struktur der damals neu vereinten Bundesrepublik ausgewählt. Die zweite Stufe umfasste die über das Einwohnermelderegister gezogene, zufallsbasierte Auswahl der Teilnehmenden nach Geschlecht und Alter in den jeweiligen sample points. Der Survey umfasste unter anderem einen Befragungsbogen, ein ärztliches Interview und die Entnahme von Blutproben. Alle Variablenkategorisierungen im Rahmen von BGS98 finden sich in Publikation 1, Seite 35 und Publikation 2, Seite 49. Grundlage der Auswahl der Teilnehmenden der KiGGS-Studie war, ähnlich zum zuvor beschriebenen Design des BGS98, ein zweistufiges stratifiziertes Cluster Sampling Design (weitere Studiendetails siehe (20)). Die 167 sample points wurden nach einem (nach Bundesländern und Gemeindetypen) geschichteten Zufallsverfahren und proportional zur Häufigkeit der Gemeindegröße gezogen. Auch der KIGGS-Survey umfasste unter anderem einen Befragungsbogen, ein ärztliches Interview und die Entnahme von Blutproben. Die Fragebögen wurden von den Eltern der Kinder (Alter ≤10 Jahre) und von den Kindern selbst (Alter >10 Jahre) ausgefüllt. Die Variablenkategorisierungen für die Auswertung der KiGGS-Basis-Daten finden sich in Publikation 3, Seite 72.

RÜCKSTELLPROBEN UND MULITPLEX SEROLOGIE

Die der Promotionsarbeit zugrundeliegenden Daten basieren auf archivierten Serumproben von BGS98 und KiGGS. Für BGS98 konnten von insgesamt 6.757 Studienteilnehmenden Serumproben abgenommen werden. Insgesamt 14.386 Teilnehmende der KIGGS-Basiserhebung im Alter von 1–17 Jahren gaben eine Serumprobe ab. In Rahmen der beiden Studien wurden nach den damaligen serologischen Untersuchungen die noch vorhandenen Serumproben als sogenannte Rückstellproben für weitere Untersuchungen bei -40°Celsius eingefroren (21). Für die vorliegenden Studien sollten 6.517 Rückstellproben von BGS98 und 12.257 von KIGGS-Basiserhebung im Jahr 2016/2017 im DKFZ getestet werden. Die Auswahl der zu testenden HPV-Typen beruhte auf folgenden Kriterien: Public Health-Relevanz, Karzinogenität nach Einteilung der Internationalen Agentur für Krebsforschung (International Agency for Research on Cancer; IARC), HPV assoziierte-Erkrankungen, Impfrelevanz, sowie eine möglichst breite Verteilung von Gattungen und Spezies (für kutane Typen) (siehe Promotionspublikation 2, Anhang, Seite 57). Insgesamt wurden neun mukosale (alpha: 6, 11, 16, 18, 31, 33, 45, 52, 58) und sieben kutane (alpha: 10; beta: 8, 38, 49; gamma: 4; nu: 41; mu: 1) HPV-

Typen einbezogen. Drei weitere mukosale Typen (35, 39, und 59) wurden zusätzlich für den BGS98 ausgewertet.

Die serologischen Tests wurden mittels eines am DKFZ entwickelten Glutathion-S-Transferase (GST) Capture Immunassay mithilfe fluoreszierender Bead Technologie durchgeführt, wie ausführlich von Waterboer et al. beschrieben (22). Der Multiplex-Assay kann Antikörper spezifisch für das Kapsidprotein L1 verschiedener HPV-Typen messen. Hierzu sind farbkodierte Beads über Gluthation-S-Transferase mit dem entsprechenden Antigen verbunden. Die Serum-Antikörper binden die Bead-gekoppelten Antigene, welche mittels sekundärer Antikörper detektiert werden. Ein spezielles Durchflusszytometer misst einerseits die Fluoreszenz, welche von den gebundenen, sekundären Antikörpern emittiert wird. Andererseits können die Antikörper spezifisch für unterschiedliche HPV-Typen mittels der jeweiligen markierten, gebundenen Beads unterschieden werden. Die Messung sekundärer Antikörper in Form der Mittleren Fluoreszenzintensität (MFI) erlaubt eine Quantifizierung der HPV-spezifischen Antikörper im Serum. Zur Berechnung der Seropositivität wurden MFI Werte auf Grundlage eines typspezifischen Grenzwerts in positiv und negativ dichotomisiert, wie ausführliche bei Clifford et al. beschrieben (23). Mit Hilfe dieses Verfahren wurden die folgenden MFI Grenzwerte bestimmt: HPV-6: 571, HPV-11: 500, HPV-16: 200, HPV-18: 200, HPV-31: 712, HPV-33: 515, HPV-35: 552, HPV-39: 200, HPV-45: 368, HPV-52: 371, HPV-58: 200, HPV-59: 200. Der Grenzwert für kutane HPV-Typen wurde bei 200 festgelegt.

Bei der CMV Serologie wurde mittels des zuvor beschriebenen Multiplex Verfahrens auf Antikörper spezifisch für vier humane CMV-Proteine (pp28, pp52, pp65 and pp150) getestet. Der Seropositivitäts-Grenzwert wurde für alle vier Proteine auf eine MFI von 150 Einheiten festgelegt. Studienteilnehmende wurden als CMV-seropositiv definiert, wenn das Signal spezifisch für zwei oder mehr CMV-Protein spezifische Antikörper über 150 MFI Einheiten lagen. Eine Validierung des CMV-spezifischen Multiplex-Assays wurde mittels Vergleiches mit dem Enzygnost Anti-CMV/IgG Assay durchgeführt und zeigte sehr gute Sensitivitäts- und Spezifitätswerte (24). Neben der Testung auf HPV- und CMV-Antikörper wurde zusätzlich auch auf Antikörper gegen andere STI (wie *Mycoplasma genitalium*, Herpes simplex Virus 2, und *Chlamydia trachomatis*) getestet.

STATISTISCHE ANALYSEN

Um die Repräsentativität der Ergebnisse auf nationaler Ebene gewährleisten zu können, wurden Survey-spezifische Gewichtungen für die Berechnung von

Seroprävalenzen verwendet. Die Gewichtungen stellten sicher, dass das Studiensample der Bevölkerungsstruktur in Deutschland von 1998 (BGS98) und 2003 (KiGGS-Basiserhebungen) in Bezug auf relevante sozialdemographische Variablen, wie Alter und Geschlecht glich (25). Neben gewichteten HPV-Seroprävalenzen für einzelne HPV-Typen wurden sie auch für in Impfstoffen enthalten HPV-Typ-Gruppen berechnet: (1) bivalent (HPV-2val: 16, 18); (2) quadrivalent (HPV-4val: 6, 11, 16, 18); (3) nonavalent (HPV-9val, 6, 11, 16, 18, 31, 33, 45, 52, 58). Die gruppenspezifischen Seroprävalenzen wurden als gewichteter Anteil der Teilnehmenden berechnet, welche seropositiv für mindestens einen in der jeweiligen Gruppe vorkommenden HPV-Typ waren.

Für die multivariablen Analysen wurden Poisson-Regressionsmodelle mithilfe des Survey Designs zur Berechnung von Prävalenz Ratios (PRs) verwendet, um mit CMV-, bzw. HPV-Seropositivität assoziierte unabhängige Faktoren zu identifizieren. Im finalen multivariablen Model wurden alle Variablen aufgenommen, die in einem rückwärts gerichteten Ausschlussverfahren (backward step approach) mit einer typspezifischen Seropositivität auf $p < 0,05$ Niveau assoziiert waren. Um Korrelationen zwischen HPV-Typen zu identifizieren, wurde der Pearson's Korrelationskoeffizient berechnet. Als geringe Korrelation wurden Werte zwischen 0,1–0,3, als moderate Korrelation Werte zwischen 0,3–0,5 sowie als starke Korrelation Werte ab 0,5 definiert. Das Datenmanagement und die statistischen Analysen wurden mit Stata, Version 14 (STATA Corp., College Station, TX, US) durchgeführt.

1.4. ERGEBNISSE

Von den BGS98-Rückstellproben konnten insgesamt 6.517 Proben erfolgreich auf HPV bzw. 6.552 erfolgreich auf CMV-Antikörper getestet und für die Seroprävalenzstudien verwendet werden. Soziodemographische Charakteristika der Studienteilnehmenden mit HPV-Serologie sind, stratifiziert nach Geschlecht, in Publikation 2, Tabelle 1, Seite 50 dargestellt. Insgesamt 12.257 KiGGS-Proben von Kindern im Alter von 1–17 Jahren konnten für die vorliegende Studie erfolgreich auf HPV-Antikörper getestet und verwendet werden (Publikation 3, Abbildung 1, Seite 73). Die soziodemographischen Charakteristika der Teilnehmenden finden sich in Publikation 3, Tabelle 1, Seite 74.

1.4.1. HPV-Seroprävalenzen und Risikofaktoren bei Erwachsenen

Seroprävalenzen mukosaler und impfrelevanter HPV-Typen

Die geschlechts- und altersstratifizierten HPV-Seroprävalenzen mit 95%-Konfidenzintervallen aller mukosalen HPV-Typen finden sich in Publikation 2, Tabelle 2, Seite 51. Alle Ergebnisse für die zusammengefassten (z.B. impfrelevanten) HPV-Typen finden sich in Publikation 2, Abbildung 2, Seite 52 und Abbildung 3, Seite 53. HPV-Seroprävalenzen bei Erwachsenen variierten stark zwischen den einzelnen Typen, wobei sechs von zwölf mukosalen HPV-Typen Prävalenzen unter 5% aufwiesen. Bis auf HPV-6 lag die Seroprävalenz für die übrigen HPV-Typen unter 10%. Die HPV-Seroprävalenzen der für die Krankheitslast wichtigsten HPV-Typen 6, 11, 16 und 18 lagen bei 12%, 4,1%, 6,7% und 6,2%. Geschlechtsspezifische Unterschiede gab es bei den mukosalen HPV-Seroprävalenzen nur bei HPV-6, -11 und -16, mit jeweils höheren Seroprävalenzen bei Frauen.

Auch die altersspezifischen Seroprävalenzen der mukosalen HPV-Typen unterschieden sich nach HPV-Typ und zeigten abweichende Altersverläufe. Bei Frauen fanden sich die niedrigsten Seroprävalenzen in den jüngsten Altersgruppen mit einem leichten Anstieg in den Altersgruppen der 30–49-Jährigen und einem konstant hohen Niveau in den älteren Altersgruppen. Die beiden HPV-Typen 6 und 35 bildeten eine Ausnahme mit niedrigsten Seroprävalenzen in den älteren Altersgruppen. Für HPV-16 zeigte sich ein zweifacher Seroprävalenz-Peak bei den (30–39- und 60–69-jährigen) Frauen. Eine ähnliche bimodale Altersverteilung zeigte sich bei HPV-6, -11 und -18. Die HPV-16-Seroprävalenzen bei Männern zeigten bei den Jüngeren nur eine leichte Zunahme mit anschließend höchsten Seroprävalenzen bei den 30–59-Jährigen. Betrachtet man die mukosalen HPV-Seroprävalenzen nach Wohnregion der Teilnehmenden, so zeigten sich nur geringe regionale Unterschiede, wie in Publikation 2, Seite 50 beschrieben.

Etwa ein Drittel (35%) der Studienteilnehmenden waren seropositiv für mindestens einen mukosalen HPV-Typen (HPV-muk) und 28% für mindestens einen Hochrisiko-HPV-Typen (HPV-HR) (siehe Publikation 2, Tabelle 3, Seite 51).

Seroprävalenzen kutaner HPV-Typen

Betrachtet man die kutanen HPV-Typen, so sieht man auch hier einen starken Unterschied je nach HPV-Typ. Die Seroprävalenzen reichten von 8,7% für HPV-41 bis 35% bei HPV-4. Neben HPV-4 fanden sich die höchste Seroprävalenzen bei den zwei kutanen HPV-Typen 1 (34%) und 8 (19%) (siehe Publikation 2, Anhang, Tabelle 2, Seite

59). Im Gegensatz zu den mukosalen HPV-Typen gab es keine signifikanten Geschlechts-Unterschiede in den Seroprävalenzen kutaner HPV-Typen. Bei der Altersverteilung zeigte sich bei vier (HPV-8, HPV-10, HPV-38 und HPV-49) von sieben kutanen HPV-Typen eine Zunahme der HPV-Seroprävalenz mit dem Alter. Dagegen wies HPV-1 mit einer stetigen Seroprävalenz-Abnahme bei zunehmendem Alter einen gegenläufigen Seroprävalenz-Trend auf.

RISIKOFAKTOREN HPV-TYP-SPEZIFISCHER SEROPOSITIVITÄT

Die Analyse von Risikofaktoren HPV-Typ-spezifischer Seropositivität wurden auf die vier im quadrivalenten Impfstoff vorkommenden HPV-Typen sowie auf die HPV-HR- und HPV-LR-Gruppe beschränkt. Die bei den Frauen im finalen multivariaten HPV-16-Modell enthaltenen Variablen Seropositivität für mindestens einen der drei im Panel getesteten sexuell übertragbaren Infektionserreger (STI+), Anzahl bisheriger Sexualpartner*innen, Alter und Urbanität waren mit Ausnahme des Alters signifikant mit HPV-16 Seropositivität assoziiert. Bei Männern waren in der multivariablen Analyse ähnlich zu den Frauen nur STI+ und Anzahl bisheriger Sexualpartner*innen mit einer höheren HPV-16-Seropositivität assoziiert (Publikation 2, Tabelle 4, Seite 53). Alle weiteren Ergebnisse finden sich in Publikation 2, Anhang, Tabellen 4–8, Seite 61–65.

1.4.2. HPV-Seroprävalenzen und Risikofaktoren bei Kindern und Jugendlichen

SEROPRÄVALENZEN MUKOSALER UND IMPFRELEVANTER HPV-TYPEN

Einen zusammenfassenden Überblick über die Ergebnisse der Seroprävalenzen mukosaler HPV-Typen bei Kindern und Jugendlichen in KiGGS finden sich in Publikation 3, Abbildung 2, Seite 75, Publikation 3, Anhang, Tabelle 1, Seite 85 und Publikation 3, Anhang, Abbildung 2, Seite 90.

Der für die Karzinomentwicklung bedeutendste HPV-Typ 16 hatte eine relativ geringe HPV-Seroprävalenz von 2,6%, welche generell auf einem niedrigen Niveau lag und erst bei den 14–15-Jährigen auf 3,1% und 4,4% bei den 16–17-Jährigen stieg. Mit Ausnahme von HPV-6 reichte die Seroprävalenz der restlichen mukosalen HPV-Typen von 0,6% (HPV-33) bis 6,4% (HPV-31), ohne signifikante Geschlechtsunterschiede.

HPV-6 unterschied sich stark von den anderen untersuchten mukosalen HPV-Typen und wies mit 25% eine deutlich höhere Seroprävalenz auf, mit etwas niedrigeren Werten bei Mädchen (23%) im Vergleich zu Jungen (26%; $p < 0.001$). Betrachtet man die

Altersverteilung der HPV-6-Seroprävalenzen, so zeigte sich der höchste Wert (34%) in der Altersgruppe 4–6 Jahre mit einer darauf wieder sinkenden Seroprävalenz. Eine ähnliche Altersverteilung fand sich bei HPV-11.

Die anderen mukosalen HPV-Typen 18, 33, 45, 52 und 58 zeigten ähnliche Altersverteilungen mit höheren Seroprävalenzen in den älteren Altersgruppen auf jedoch insgesamt niedrigem Niveau. Gegensätzlich verhielt sich HPV-31 mit höchsten HPV-Seroprävalenzen bei den Kindern und danach stark abnehmenden Werten. Die Seroprävalenz der impfrelevanten HPV-Typen verteilte sich wie folgt: 6,1% der Kinder und Jugendlichen waren seropositiv für mindestens einen im bivalenten Impfstoff (HPV-2val) enthaltenen HPV-Typen 16 und 18. Aller weiteren Ergebnisse zu den impfrelevanten HPV-Gruppen finden sich in Publikation 3, Seite 73.

SEROPRÄVALENZEN KUTANER HPV-TYPEN

Ein zusammenfassender Überblick über die wichtigsten Ergebnisse der Seroprävalenzen kutaner HPV-Typen KiGGS findet sich hier: Publikation 3, Abbildung 3, Seite 75 und Publikation 3, Anhang, Tabelle 2, Seite 85. Zusätzlich sind die MFI-Verteilungen aller kutanen HPV-Typen dargestellt (Publikation 3, Anhang, Abbildung 3, Seite 91). Auch bei Kindern und Jugendlichen wiesen die kutanen HPV-Typen große Differenzen der Seroprävalenzen auf und reichten von 4,0% bis 8,1% bei den HPV-Typen 38, 8, 10, 41 und 49, bis hin zu 14% bei HPV-4 und 32% bei HPV-1. HPV-1 wies als einziger HPV-Typ auch einen signifikanten Geschlechtsunterschied (Mädchen: 34%; Jungen: 30%; $p < 0,001$) auf. Die Altersverteilungen waren bei allen kutanen HPV-Typen ähnlich mit niedrigsten Seroprävalenzen in den jüngsten Jahren und einem darauffolgenden nahezu stetigen Anstieg zu höchsten Seroprävalenzen in der ältesten Altersgruppe.

RISIKOFAKTOREN HPV-TYP-SPEZIFISCHER SEROPOSITIVITÄT

Die Analyse von Risikofaktoren HPV-Typ-spezifischer Seropositivität bei Kindern und Jugendlichen wurde auf die vier im quadrivalenten Impfstoff vorkommenden HPV-Typen sowie auf die kutane HPV-Gruppe (HPV-kut) beschränkt. Im Folgenden wird nur auf Risikofaktoren von Seropositivität für HPV-16 und HPV-kut eingegangen (Publikation 3, Tabelle 2, Seite 76 und Publikation 3, Tabelle 3, Seite 77). Alle weiteren Ergebnisse lassen sich im Publikationsanhang finden (Publikation 3, Anhang, Tabellen 3-5, Seite 87-89). Im multivariaten Modell waren nur Alter und Wohnregion signifikant mit HPV-16-Seropositivität assoziiert (Publikation 3, Tabelle 2, Seite 76). Im multivariablen HPV-kut-

Modell waren Alter, Wohnregion, Urbanität und Migrationshintergrund der Eltern mit HPV-kut-Seropositivität assoziiert (Publikation 3, Tabelle 3, Seite 77).

1.4.3. CMV-Seroprävalenz und Risikofaktoren bei Erwachsenen

Die Ergebnisse der CMV-Seroprävalenzstudie beruhen auf insgesamt 6.552 Teilnehmenden mit CMV-Serologie. Die für die Bevölkerung in Deutschland repräsentative CMV-Seroprävalenz wurde auf 57% geschätzt. Die CMV-Seroprävalenz unterschied sich dabei stark nach Geschlecht, mit einer CMV-Seroprävalenz von 62% bei Frauen und 51% bei Männern (Publikation 1, Abbildung 1, Seite 38). Bei Frauen im gebärfähigen Alter (18–45 Jahre) lag die CMV-Seroprävalenz bei 52%. Die CMV-Seroprävalenz stieg sowohl bei Frauen als auch bei Männern mit zunehmendem Alter an. Neben dem Geschlechtsunterschied gab es auch deutliche Unterschiede in der CMV-Seroprävalenz zwischen den verschiedenen Regionen in Deutschland. Die CMV-Seroprävalenz lag sowohl für Frauen (66%) als auch für Männer (52%) im Norden von Deutschland höher als in Süddeutschland (Frauen: 57%; Männer: 47%).

Ergebnisse der multivariaten Analyse finden sich in Publikation 1, Tabelle 2, Seite 38. Die folgenden Faktoren waren sowohl bei Frauen als auch bei Männern mit CMV-Seropositivität assoziiert: zunehmendes Alter, Geburtsland außerhalb Deutschlands, Rauchen, wohnhaft in Norddeutschland, zunehmende Anzahl von Haushaltsmitgliedern unter 18 Jahren, und niedriger Bildungsstatus. Weitere Assoziationen einer CMV-Seropositivität waren für Frauen: zunehmende Anzahl von Geschwistern im gleichen Haushalt sowie Wohnort in Ostdeutschland. Nur für Männer war der Besuch einer Kindertagesstätte in der Kindheit negativ mit CMV-Seropositivität assoziiert.

1.5. Diskussion

1.5.1. HPV-Seroepidemiologie bei Erwachsenen, Kindern und Jugendlichen

Wie hoch ist die Seroprävalenz von Antikörpern gegen verschiedene HPV-Typen in der deutschen Bevölkerung?

Mit einer Seroprävalenz von 6,7% war HPV-16 in der erwachsenen Studienpopulation von BGS98 der häufigste impfrelevante HPV-Hochrisikotyp, was auch in anderen HPV-Studien gezeigt wurde (siehe Publikation 2, Diskussion, Seite 52). Allerdings sind für

den Vergleich von serologischen Ergebnissen, neben methodologischen Serologie-Unterschieden (wie im Abschnitt HPV-Serologie, Seite 19 diskutiert), auch regionale Differenzen der HPV-16-Verbreitung zu beachten, so dass die jeweilige Höhe der HPV-16-Seroprävalenz, trotz typspezifischer Dominanz, eine starke Variabilität in weltweiten Serologie-Studien (aber auch DNA-Studien) aufweisen kann (26).

Die KIGGS-Daten ergaben eine zu erwartende niedrigere HPV-16-Seroprävalenz von 2,6%. Generell zeigten die HPV-16-Seroprävalenzen bei Kindern und Jugendlichen eine vergleichbare Höhe wie ähnliche Studien, obgleich auch weltweite methodisch-ähnliche serologische HPV-16-Prävalenzdaten bei Kindern und Jugendlichen eine hohe Variabilität von 0–11% aufzeigen, wie ausführlich in Publikation 3, Seite 78, beschrieben. Etwa ein Viertel der Erwachsenen hatte Antikörper gegen mindestens einen HPV-9val-Typen. Die Verbreitung von Antikörpern gegenüber mindestens einen mukosalen HPV-HR-Typ lag bei Kindern und Jugendlichen bei etwa 13%, mit einem Großteil der typspezifischen HPV-Seroprävalenz von jeweils unter 3%.

Im Vergleich zu mukosalen HPV-Typen waren Antikörper gegen kutane HPV-Typen im Durchschnitt deutlich häufiger zu finden. Mit knapp 35% hatten HPV-1 und HPV-4 die höchsten Seroprävalenzen unter den Erwachsenen. Die HPV-Seroprävalenz von kutanen Typen, und vor allem bei HPV-1 und HPV-4, lag auch bei Kindern und Jugendlichen deutlich höher und verweist auf das von ihnen (neben HPV-2) verursachte, häufige Krankheitsbild der gewöhnlichen Haut-, Fußsohlen- und Plantarwarzen.

GIBT ES EINEN GESCHLECHTS-UNTERSCHIED DER HPV-SEROPRÄVALENZEN?

Die vorliegenden Ergebnisse der mukosalen HPV-Typen zeigen einen (moderaten) Seroprävalenz-Geschlechts-Unterschied bei den Erwachsenen, mit etwas höheren mukosalen Seroprävalenzen bei den Frauen. Dies wird teilweise auch in anderen Studien berichtet, wie in Publikation 2, Seite 54 erläutert und anhand diverser biologischer Faktoren, wie beispielsweise Epithelunterschieden der Infektionsstelle, diskutiert. Der Geschlechtsunterschied war bei KiGGS mit Ausnahme von HPV-6 nicht vorhanden. Im Vergleich zu den mukosalen HPV-Typen wurden weder im BGS98 noch in KiGGS Geschlechtsunterschiede in der Höhe der kutanen HPV-Seroprävalenzen nachgewiesen.

GIBT ES EINEN ALTERS-UNTERSCHIED DER HPV-SEROPRÄVALENZEN?

Der hauptsächlich bei Frauen beobachtete leichte Anstieg der HPV-HR-Seroprävalenz in den jüngsten Altersgruppen war zu erwarten und spiegelt den Beginn bzw. die Zunahme der sexuellen Aktivität wider und stimmt auch mit anderen Seroprävalenzstudien

überein (27). Eine bereits relativ hohe HPV-HR-Seroprävalenz von fast 10% bei den 18–24-Jährigen unterstreicht dabei die Bedeutung der Impfung in jungen Jahren, insbesondere vor dem sexuellen Debüt.

Betrachtet man die serologischen Ergebnisse bei Kindern und Jugendlichen im KiGGS-Basis Survey, so konnte doch eine gewisse Antikörper-Höhe bestimmter mukosaler HPV-Typen, wie HPV-6, HPV-11, und HPV-31, bei Kindern im mittleren Alter beobachtet werden – in einer Alterspanne über dem Alter des Vorhandenseins mütterlicher (durch eine potentiell vertikale Übertragung erworbener) Antikörper und unter dem Alter, in dem sie bereits sexuell aktiv sind und HPV-Antikörper durch sexuellen Kontakt entstanden wären. Vergleicht man die Daten mit anderen Studien, so zeigt sich zumindest bei HPV-6-DNA Studien ein ähnlicher Trend mit hohen Prävalenzen bereits bei den jüngsten Altersgruppen (28).

Eine HPV-16-Antikörper-Zunahme zeigte sich in unserer Studie ab etwa 14 Jahren, entsprechend des Beginns sexueller Aktivitäten, wie es auch von vielen anderen Studien gezeigt wurde (29-31). Diese Altersverteilung wurde auch bei den meisten anderen mukosalen HPV-Typen beobachtet. Im Vergleich zu den kutanen HPV-Typen zeigten die meisten Kinder jedoch eher niedrige mukosale Seroprävalenzen. Trotz der im allgemeinen niedrigen mukosalen HPV-Seroprävalenzen bei Kindern und Jugendlichen, zeigen die vorliegenden Ergebnisse jedoch, dass bereits Kinder vor der Pubertät gegenüber HPV-HR-Typen exponiert waren. Dies wurde bereits in anderen Studien beobachtet und kann nicht allein, wie ursprünglich gedacht, auf Übertragungen durch sexuellen Missbrauch erklärt werden, wie von Syrjänen (2010) diskutiert (7). Hier müssen diverse Übertragungswege, wie pre- und perinatale, horizontale Übertragungen, aber auch die sogenannte Autoinokulation, also die Selbstinfektion anderer bisher noch nicht infizierter Körperstellen, in Betracht gezogen werden (7).

Die Ergebnisse der typ- und altersspezifischen Seroprävalenz von kutanen HPV-Typen bei Erwachsenen waren vergleichbar mit anderen Studien mit einem altersbedingten Anstieg der meisten kutanen HPV-Typen mit Ausnahme von HPV-1 (32, 33). Da HPV-1- und HPV-4-bedingte Warzen bei Kindern und Jugendlichen sehr häufig vorkommen, war die hohe Prävalenz von HPV-1 und HPV-4 bei den jüngsten Teilnehmenden des Erwachsenensurveys zu erwarten (32). Dieser Trend entspricht der typischen Verbreitung von HPV-assoziierten Warzen, wie bereits zuvor beschrieben.

WELCHE SOZIODEMOGRAPHISCHEN UND VERHALTENSBASIERTEN FAKTOREN SIND MIT EINER HPV-SEROPOSITIVITÄT ASSOZIIERT?

In der Analyse von HPV-Risikofaktoren bei den Erwachsenen waren sowohl STI+ als auch die Anzahl bisheriger Sexualpartner*innen die stärksten Faktoren, die mit der HPV-16-Seropositivität assoziiert waren, wie auch in anderen Studien gezeigt und in Publikation 2, Seite 54 diskutiert.

Bei den Kindern und Jugendlichen war das Alter am stärksten mit HPV-16-Seropositivität assoziiert, was, wie bereits von anderen Studien gezeigt, auf den Beginn des Sexuallebens hinweist. Daneben war der Wohnort in Westdeutschland im Vergleich zu Ostdeutschland ebenfalls mit einer höheren HPV-16-Seroprävalenz assoziiert. Da dies sowohl bei den mukosalen HPV-Typen 6, 11, 16 and 18 als auch im HPV-kut-Modell gezeigt werden konnte, könnte dies regionale und kulturelle Unterschiede zwischen der BRD und der DDR (1949 bis 1990) widerspiegeln, welche auf unterschiedliche Weise Einfluss auf die Übertragungswege (auch in Bezug auf andere Infektionskrankheiten, siehe Publikation 1) haben könnten. Wenngleich regionale Seroprävalenz-Unterschiede bekannt sind, können hierfür keine konkreten Erklärungen gegeben werden und müssten ggf. weitergehend mit Hilfe verhaltensbasierter Analysen untersucht werden.

1.5.2. CMV-SEROEPIDEMIOLOGIE BEI ERWACHSENEN

WIE HOCH IST DIE SEROPRÄVALENZ VON CMV-ANTIKÖRPERN IN DER DEUTSCHEN BEVÖLKERUNG?

Vergleicht man die von uns im BGS98 gemessene CMV-Seroprävalenz der Erwachsenen in Höhe von 57% mit anderen europäischen Ländern, wie Portugal, Schweden oder Kroatien, so finden sich dort etwas höhere Prävalenzen von 77–83% (34-36).

GIBT ES EINEN GESCHLECHTS-UNTERSCHIED DER CMV-SEROPRÄVALENZ?

Bei CMV konnte im Vergleich zu HPV ein starker geschlechtsspezifischer Unterschied mit höheren Seroprävalenzen in Frauen im Vergleich zu Männern gezeigt werden, welcher sich auch in anderen Studien widerspiegelt (37, 38).

GIBT ES EINEN ALTERS-UNTERSCHIED DER CMV-SEROPRÄVALENZ?

CMV-Seroprävalenz nahm mit zunehmendem Alter fast stetig zu. Betrachtet man allein Frauen im gebärfähigen Alter (18–45 Jahre), so waren etwa 52% CMV-seropositiv.

WELCHE SOZIODEMOGRAPHISCHEN UND VERHALTENSBASIERTEN FAKTOREN SIND MIT EINER CMV-SEROPOSITIVITÄT ASSOZIIERT?

In unserer Studie war Alter einer der beiden stärksten unabhängigen Faktoren, die sowohl bei Frauen als auch Männern mit einer CMV-Seropositivität assoziiert waren. Der Anstieg der CMV-Seroprävalenz mit zunehmendem Alter ist bekannt und resultiert aus einer lebenslangen, kumulativen CMV-Exposition. Der andere Faktor war das Geburtsland außerhalb Deutschlands. Länderspezifische Seroprävalenzunterschiede können durch Unterschiede in der Häufigkeit der wichtigsten Expositionen im Zusammenhang mit der CMV-Übertragung erklärt werden: Häufigkeit und Dauer des Stillens, Bevölkerungsdichte, Kinderbetreuungseinrichtungen und Sexualverhalten (10). Beide Assoziationsfaktoren wurden auch bereits in Studien aus anderen Ländern nachgewiesen (39).

1.5.3. STÄRKEN UND LIMITATIONEN

SEROLOGIE VON HPV

Die Analyse von HPV-Antikörpern ist eine anerkannte Methodik zur Messung kumulativer HPV-Exposition. Allerdings gibt es einige Limitationen zur Aussagekraft serologischer Analysen und Ergebnisse, die in der Interpretation auch der vorliegenden Daten stets mitbedacht werden müssen.

HPV-Serologie führt zum einen grundsätzlich zu einer Untererfassung der tatsächlichen HPV-Exposition, da nicht alle Menschen nach einer HPV-Infektion auch serokonvertieren und darüber hinaus auch das Antikörper-Waning mit in Betracht gezogen werden muss (40, 41). Hinzukommt, dass sich sowohl die Latenzzeit, die Serokonversionsrate als auch das Ausmaß des Antikörper-Wanings je nach HPV-Typ, aber auch nach Geschlecht und Alter der infizierten Person oder nach der jeweiligen Infektionsstelle unterscheiden können, wie ausführlich in Publikation 2, Seite 54 und Publikation 3, Seite 79 diskutiert.

Zum anderen steht insbesondere die HPV-Serologie vor einer methodologischen Herausforderung, da verschiedene Assays auch verschiedene Antigen-Aufbereitungen (zum Beispiel der Virusartigen Partikel, VLP) und Grenzwert-Definitionen verwenden. Somit gibt es diverse serologische HPV-Antikörper-Nachweismethoden, gleichzeitig aber keine universell anwendbaren Referenzen bzw. Standard-Grenzwerte für die unterschiedlichen HPV-Typen. Dies stellt nicht zuletzt auch eine Herausforderung in Bezug auf die Bedeutung der HPV-Serologie zur Evaluation von Impfeffektivität dar (42). Eine direkte Vergleichbarkeit zwischen serologischen HPV-Studien bleibt aus zuvor

genannten Gründen schwierig, obgleich ein Vergleich verschiedener serologischer HPV-Assays zeigen konnte, dass trotz der Unterschiede in der VLP-Qualität und der verwendeten Grenzwerte ähnlich spezifische Ergebnisse erreicht wurden (43). Der allgemeingültige Nachteil der HPV-Serologie wurde von uns insofern beachtet, dass der im Rahmen der Analyse benutzte und am DKFZ entwickelte Assay und die darin verwendeten Grenzwerte bereits in anderen Studien verwendet und evaluiert wurden (23, 42-46).

Neben diesen methodologischen Herausforderungen muss aber auch beachtet werden, dass die HPV-Seroprävalenzen starke regionale und zeitliche Unterschiede aufweisen können, die durch die jeweilige Studienbevölkerung, deren Erhebungszeitraum, aber auch die damit einhergehenden verhaltensbasierten Unterschiede, wie das Sexualverhalten, beeinflusst werden. Dies wurde auch hinsichtlich der Seroprävalenz-Unterschiede nach Wohnort im Rahmen unserer Regressionsanalysen festgestellt. Hinzu kommt insbesondere bei Kindern, dass die Studienergebnisse stark von der Alterszusammensetzung der Studienpopulation abhängen. Dies liegt vor allem am Umfang der in die Analysen einfließenden Daten von bereits sexuell aktiven Jugendlichen, die überhaupt erst die Möglichkeit hatten, über den Hauptübertragungsweg des sexuellen Kontaktes gegenüber dem Virus exponiert gewesen zu sein.

Eine weitere Einschränkung ist die potentielle Kreuzreaktivität verschiedener verwandter HPV-Typen, die entsprechend zu einer Überschätzung der Seroprävalenz einiger Typen führen könnte. Wir konnten (wie in Publikation 3, Seite 75 beschrieben) jedoch keine wesentlichen Kreuzreaktivitäten zwischen den verschiedenen HPV-Serotypen feststellen, so dass wir davon ausgehen, dass die Mehrheit unserer Ergebnisse typspezifische Seroprävalenzen widerspiegelt.

Neben den genannten Herausforderungen der HPV-Serologie bietet die angewandte Methodik jedoch auch Stärken. Mit Hilfe des vom DKFZ entwickelten Multiplex-Assays konnten zwei große repräsentative Surveys und die darin insgesamt enthaltenen 18.774 Proben in einem Labor und vom gleichen Personal gleichzeitig auf Antikörper verschiedener mukosaler und kutaner HPV-Typen untersucht werden. Durch die beiden methodologisch als repräsentativ aufgestellten Bevölkerungssurveys konnten die serologischen Ergebnisse mit entsprechenden soziodemographischen und verhaltensbasierten Daten analysiert werden. Die Nutzung bereits erhobener Daten und darauf aufbauende weiterführende Analysen stellen somit auch eine effektive und ressourcenschonende

Generierung epidemiologischer Daten dar, aus denen wiederum potentiell neue Rückschlüsse zu Public Health-Maßnahmen geschlossen werden können.

Des Weiteren basieren HPV-Prävalenzdaten aus Deutschland zumeist auf DNA-Proben (47-49). Bisherige (weltweite) HPV-Seroprävalenzstudien fokussieren dagegen primär auf die erwachsene Bevölkerung, oder ggf. noch Jugendliche (siehe Diskussion in Publikation 3, Seite 78). Mit Hilfe der KiGGS-Daten und des Multiplex-Assays konnten nun erstmalig serologische HPV-Daten von Kindern und Jugendlichen im Alter von 1–17 Jahren in einem (repräsentativen) Umfang generiert und analysiert werden.

SEROLOGIE VON CMV

Im Vergleich zur HPV-Methodik liegt für CMV eine Validitätsstudie des verwendeten Assays mit einer jeweils hohen Sensitivität und Spezifität vor. Die größte Stärke der vorliegenden Studie – äquivalent zu den HPV-Daten – liegt damit in der Verwendung von bevölkerungsbasierten repräsentativen Proben zur Bestimmung der CMV-Seroprävalenz und der damit möglichen Analyse soziodemographischer und verhaltensbasierter Risikofaktoren.

Eine wichtige Einschränkung ist jedoch die begrenzte Übertragbarkeit auf die aktuelle CMV-Verbreitung in Deutschland aufgrund der relativ alten Datenbasis von BGS98. Trotzdem können die Daten als wichtige Grundlage zu den zuvor genannten Public Health-Maßnahmen dienen, da sich die CMV-Seroprävalenzen und vor allem die alters- und geschlechtsspezifischen Unterschiede in den letzten 20–25 Jahren wahrscheinlich kaum grundlegend verändert haben, wie ausführlich in Publikation 1, Seite 39 diskutiert. Trotzdem wären aktuelle und longitudinale Studien zur Entwicklung von CMV in Deutschland hilfreich. Gerade die serologischen Untersuchungen des BGS98 könnten hierfür als Grundlage einer longitudinalen Analyse mit Hilfe des vom RKI in der Folge durchgeführten Bevölkerungssurveys DEGS1 genutzt werden.

1.5.4. ZUSAMMENFASSUNG UND AUSBLICK

Die vorliegenden Daten stellen die ersten repräsentativen Daten zur Seroepidemiologie von einer großen Auswahl mukosaler und kutaner HPV-Typen in Deutschland dar. Durch die Verwendung der Bevölkerungssurveys BGS98 und KiGGS, welche vor der Einführung der HPV-Impfung durchgeführt wurden, konnten Basisdaten für natürlich und kumulativ erworbene typspezifische HPV-Exposition der deutschen nicht-geimpften Bevölkerung generiert werden. Die Untersuchung typspezifischer HPV-Exposition trägt

zum Wissensstand der bisherigen Verbreitung von HPV bzw. deren im Rahmen der Studie untersuchten unterschiedlichen HPV-Serotypen in verschiedenen Bevölkerungsgruppen bei. Die Regressionsanalysen der Seropositivität und deren Identifikation von Risikofaktoren trägt ebenfalls zu einem erweiterten Kenntnisstand zu potentiellen Risiko- und Präventionsfaktoren von HPV in Deutschland bei.

Für Kinder und Jugendliche ist der Kenntnisstand zur HPV-Seroepidemiologie insbesondere in Bezug auf die Relevanz des altersspezifischen HPV-Impfschemas von großer Bedeutung. Bisherige Daten zur Impfabdeckung zeigen, dass die vollständige HPV-Impfung unter 15-jährigen Mädchen noch immer relativ gering ist, wenngleich sie bis 2018 auf 43% stieg (50). Aufgrund der leichten sexuellen Übertragbarkeit von HPV wird die Impfung für Mädchen und Jugendliche grundsätzlich vor Beginn des Sexualitätslebens empfohlen. Die Studienergebnisse zur HPV-Seroprävalenz zeigen jedoch, dass bereits ein gewisser Anteil von Kindern über HPV-Antikörper gegen impfpräventable HPV-Typen verfügt, noch vor dem Beginn sexueller Aktivität. Die hier gezeigte frühe HPV-Exposition wäre daher, als weiteres Argument einer früher ansetzenden HPV-Impfung zu diskutieren (9).

Auch für CMV stellt die vorliegende Publikation die erste repräsentative bevölkerungsbezogene Studie zur CMV-Seroepidemiologie der deutschen erwachsenen Wohnbevölkerung dar. Die Daten tragen zum Verständnis der Verbreitung von CMV in verschiedenen Bevölkerungsgruppen aber auch über Risikofaktoren einer CMV-Exposition bei. Dies ist insofern Public Health-relevant, als dass insbesondere kongenitale, also pränatale, CMV-Infektionen mit schweren Komplikationen und Gesundheitsrisiken für die (ungeborenen) Kinder verbunden sind, wie ausführlich in der Diskussion in Publikation 1, Seite 39 beschrieben.

Im Unterschied zu HPV existiert bis heute jedoch kein zugelassener CMV-Impfstoff, obgleich verschiedene CMV-Impfstoffe bereits in Entwicklung sind. Ein CMV-Impfstoff hätte zum einen das Ziel, kongenitale CMV-Infektion zu reduzieren, zum anderen könnte er aber auch dazu beitragen, die potentiell höheren Risiken einer CMV-Infektion und deren gesundheitliche Auswirkungen unter Immunsupprimierten und der älteren Bevölkerung zu minimieren (51). Um Public Health-Empfehlungen in Bezug auf die Anwendungsstrategien eines potentiellen CMV-Impfstoffs zu entwickeln, sind repräsentative epidemiologische alters- und geschlechtsstratifizierte Daten über die bisherige CMV-Verbreitung und Belastung durch CMV-Infektionen in der deutschen Bevölkerung

unerlässlich. Da für Deutschland bis dato keine solchen populationsbasierten Seroprävalenzdaten für CMV-Antikörper vorlagen, wurde die vorliegende Studie durchgeführt. Die durch die Studie generierten seroepidemiologischen Ergebnisse zur Verbreitung der kumulativen CMV-Exposition in der Bevölkerung in Deutschland können daher im Rahmen von Übertragungsmodellen zukünftige Impfstrategien unterstützen.

Gleichzeitig müssen, solange eine Impfung nicht zur Verfügung steht, alternative CMV-Präventionsmaßnahmen ergriffen werden. Dies ist umso wichtiger, da, wie in unseren Ergebnissen dargestellt, etwa die Hälfte der untersuchten Frauen im gebärfähigen Alter noch CMV-seronegativ waren und somit weiterhin suszeptibel für eine CMV-Infektion in der Schwangerschaft waren. Gleichzeitig ist jedoch relativ wenig über CMV in der Allgemeinbevölkerung bekannt. Hier wären präventive Maßnahmen wie Aufklärung zu CMV-Infektionen, die Bedeutung und Folgen für Kinder sowie Hygiene-spezifische Präventionsaufklärung unter Schwangeren eine sinnvolle und notwendige Public Health Maßnahme, solange keine zugelassenen Impfstoffe verfügbar sind. Insbesondere, da ein CMV-Antikörpertest in der Schwangerschaft von den Krankenkassen in der Regel nicht übernommen wird. Zukünftige CMV-Seroprävalenzstudien könnten hierbei ansetzen und anhand aktueller Daten die Entwicklung von CMV-Seroprävalenzen und ggf. Public Health-Maßnahmen zur Vorbeugung von CMV-Infektionen insbesondere in Hochrisikogruppen untersuchen und evaluieren.

Im Rahmen der vorliegenden Arbeit konnten erfolgreich insgesamt über 18.000 Rückstellproben von Erwachsenen, Kindern und Jugendlichen aus Deutschland auf HPV- und CMV-Antikörper untersucht und die Ergebnisse weitergehend analysiert werden. Die Ergebnisse können, trotz der zuvor beschriebenen bedingten Limitationen ihrer Aussagekraft, unter anderem durch die Größe und Repräsentativität der zugrunde liegenden Surveydaten einen wichtigen Beitrag leisten, den Wissenstand zu HPV und CMV zu erweitern. Darüber hinaus können die Ergebnisse zur Evaluation und Anpassung bestehender und zukünftiger Public Health-Maßnahmen zur Prävention von HPV- und CMV-Infektionen genutzt werden.

1.6. LITERATURVERZEICHNIS

1. Beitz R, Bergmann E, Bergmann KE, Hermann-Kunz E, Kamtsiuris P, Kurth B-M, Melchert H-U, Mensink GBM, Stolzenberg H, Thamm M, Thefeld W, Thierfelder W, Wagner C, Ziese T. Der Bundes-Gesundheitssurvey – Baustein der Gesundheitssurveillance in Deutschland. Berlin: Robert Koch-Institut; 2002. Report No.: 3-89606-135-6.
2. Kurth B-M, Kamtsiuris P, Hölling H, Schlaud M, Dölle R, Ellert U, Kahl H, Knopf H, Lange M, Mensink GBM, Neuhauser H, Rosario AS, Scheidt-Nave C, Schenk L, Schlack R, Stolzenberg H, Thamm M, Thierfelder W, Wolf U. The challenge of comprehensively mapping children's health in a nation-wide health survey: Design of the German KiGGS-Study. BMC public health. 2008;8(1):196.
3. Mauz E, Lange M, Houben R, Hoffmann R, Allen J, Gößwald A, Hölling H, Lampert T, Lange C, Poethko-Müller C, Richter A, Rosario AS, von Schenck U, Ziese T, Kurth B-M, Team tKCR. Cohort profile: KiGGS cohort longitudinal study on the health of children, adolescents and young adults in Germany. International journal of epidemiology. 2019.
4. de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H. Classification of papillomaviruses. Virology. 2004;324(1):17-27.
5. International Agency for Research on Cancer (WHO). Biological Agents - Human Papillomaviruses. IARC monographs on the evaluation of carcinogenic risks to humans. 2012;Volume 100 B. A review of human carcinogens.:255-313.
6. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet. 2007;370(9590):890-907.
7. Syrjanen S. Current concepts on human papillomavirus infections in children. APMIS : acta pathologica, microbiologica, et immunologica Scandinavica. 2010;118(6-7):494-509.
8. Hufbauer M, Akgül B. Molecular Mechanisms of Human Papillomavirus Induced Skin Carcinogenesis. Viruses. 2017;9(7):187.
9. Cason J, Mant CA. High-risk mucosal human papillomavirus infections during infancy & childhood. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2005;32 Suppl 1:S52-8.
10. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Reviews in medical virology. 2010;20(4):202-13.
11. Enders G, Bäder U, Bartelt U, Daiminger A. Zytomegalievirus- (CMV-) Durchseuchung und Häufigkeit von CMV-Primärinfektionen bei schwangeren Frauen in Deutschland. Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz. 2003;46(5):426-32.
12. Kowalzik F, Hitzler W, Runkel S, Marron M. Seroprevalence and Seroconversion of Cytomegalovirus in a Large Group of Healthy, German Blood Donors: Potential Contribution to Transfusion Transmitted Infections. Clinical laboratory. 2020;66(4).
13. Hecker M, Qiu D, Marquardt K, Bein G, Hackstein H. Continuous cytomegalovirus seroconversion in a large group of healthy blood donors. Vox Sanguinis. 2004;86(1):41-4.
14. Griffiths PD. Burden of disease associated with human cytomegalovirus and prospects for elimination by universal immunisation. The Lancet Infectious diseases. 2012;12(10):790-8.
15. Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. Clinical microbiology reviews. 2013;26(1):86-102.

16. Binda S, Pellegrinelli L, Terraneo M, Caserini A, Primache V, Bubba L, Barbi M. What people know about congenital CMV: an analysis of a large heterogeneous population through a web-based survey. BMC infectious diseases. 2016;16(1):513.
17. Loenenbach AD, Poethko-Muller C, Pawlita M, Thamm M, Harder T, Waterboer T, Schroter J, Delere Y, Wichmann O, Wiese-Posselt M. Mucosal and cutaneous Human Papillomavirus seroprevalence among adults in the prevaccine era in Germany - Results from a nationwide population-based survey. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2019;83:3-11.
18. Loenenbach A, Pawlita M, Waterboer T, Harder T, Poethko-Muller C, Thamm M, Lachmann R, Delere Y, Wichmann O, Wiese-Posselt M. Seroprevalence of mucosal and cutaneous human papillomavirus (HPV) types among children and adolescents in the general population in Germany. BMC infectious diseases. 2022;22(1):44.
19. Lachmann R, Loenenbach A, Waterboer T, Brenner N, Pawlita M, Michel A, Thamm M, Poethko-Muller C, Wichmann O, Wiese-Posselt M. Cytomegalovirus (CMV) seroprevalence in the adult population of Germany. PloS one. 2018;13(7):e0200267.
20. Kurth BM, Kamtsiuris P, Holling H, Schlaud M, Dolle R, Ellert U, Kahl H, Knopf H, Lange M, Mensink GB, Neuhauser H, Rosario AS, Scheidt-Nave C, Schenk L, Schlack R, Stolzenberg H, Thamm M, Thierfelder W, Wolf U. The challenge of comprehensively mapping children's health in a nation-wide health survey: design of the German KiGGS-Study. BMC public health. 2008;8:196.
21. Thierfelder W, Dortschy R, Hintzpeter B, Kahl H, Scheidt-Nave C. Biochemische Messparameter im Kinder- und Jugendgesundheitssurvey (KiGGS). Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz. 2007;50(5):757-70.
22. Waterboer T, Sehr P, Michael KM, Franceschi S, Nieland JD, Joos TO, Templin MF, Pawlita M. Multiplex human papillomavirus serology based on in situ-purified glutathione s-transferase fusion proteins. Clin Chem. 2005;51(10):1845-53.
23. Clifford GM, Shin HR, Oh JK, Waterboer T, Ju YH, Vaccarella S, Quint W, Pawlita M, Franceschi S. Serologic response to oncogenic human papillomavirus types in male and female university students in Busan, South Korea. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2007;16(9):1874-9.
24. Brenner N, Mentzer AJ, Butt J, Michel A, Prager K, Brozy J, Weissbrich B, Aiello AE, Meier HCS, Breuer J, Almond R, Allen N, Pawlita M, Waterboer T. Validation of Multiplex Serology detecting human herpesviruses 1-5. PloS one. 2018;13(12):e0209379.
25. Kurth BM, Bergmann KE, Holling H, Kahl H, Kamtsiuris P, Thefeld W. [The National Child and Adolescent Health Survey. The complete concept]. Gesundheitswesen (Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany)). 2002;64 Suppl 1:S3-11.
26. Vaccarella S, Franceschi S, Clifford GM, Touze A, Hsu CC, de Sanjose S, Pham TH, Nguyen TH, Matos E, Shin HR, Sukvirach S, Thomas JO, Boursaghin L, Gaitan J, Snijders PJ, Meijer CJ, Munoz N, Herrero R, Coursaget P. Seroprevalence of antibodies against human papillomavirus (HPV) types 16 and 18 in four continents: the International Agency for Research on Cancer HPV Prevalence Surveys. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2010;19(9):2379-88.

27. Liu G, Markowitz LE, Hariri S, Panicker G, Unger ER. Seroprevalence of 9 Human Papillomavirus Types in the United States, 2005-2006. The Journal of infectious diseases. 2016;213(2):191-8.
28. Syrjänen S, Rintala M, Sarkola M, Willberg J, Rautava J, Koskimaa H, Paaso A, Syrjänen K, Grénman S, Louvanto K. Oral Human Papillomavirus Infection in Children during the First 6 Years of Life, Finland. Emerging Infectious Disease journal. 2021;27(3):759.
29. Kramer M, Mollema L, Smits G, Boot H, de Melker H, van der Klis F. Age-specific HPV seroprevalence among young females in The Netherlands. Sexually transmitted infections. 2010;86(7):494-9.
30. Jit M, Vyse A, Borrow R, Pebody R, Soldan K, Miller E. Prevalence of human papillomavirus antibodies in young female subjects in England. British journal of cancer. 2007;97(7):989-91.
31. Ryding J, French KM, Naucler P, Barnabas RV, Garnett GP, Dillner J. Seroepidemiology as basis for design of a human papillomavirus vaccination program. Vaccine. 2008;26(41):5263-8.
32. Antonsson A. Review: antibodies to cutaneous human papillomaviruses. Journal of medical virology. 2012;84(5):814-22.
33. Rahman S, Pierce Campbell CM, Waterboer T, Rollison DE, Ingles DJ, Torres BN, Michel A, Sudenga SL, Pawlita M, Villa LL, Lazcano Ponce E, Borenstein AR, Wang W, Giuliano AR. Seroprevalence of cutaneous human papillomaviruses (HPV) among men in the multinational HIM Study. J Gen Virol. 2016.
34. Lopo S, Vinagre E, Palminha P, Paixao MT, Nogueira P, Freitas MG. Seroprevalence to cytomegalovirus in the Portuguese population, 2002-2003. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2011;16(25).
35. Vilibic-Cavlek T, Kolaric B, Beader N, Vrtar I, Tabain I, Mlinaric-Galinovic G. Seroepidemiology of cytomegalovirus infections in Croatia. Wiener klinische Wochenschrift. 2017;129(3-4):129-35.
36. Olsson J, Kok E, Adolfsson R, Lovheim H, Elgh F. Herpes virus seroepidemiology in the adult Swedish population. Immun Ageing. 2017;14:10.
37. Korndewal MJ, Mollema L, Tcherniaeva I, van der Klis F, Kroes AC, Oudesluys-Murphy AM, Vossen AC, de Melker HE. Cytomegalovirus infection in the Netherlands: seroprevalence, risk factors, and implications. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2015;63:53-8.
38. Antona D, Lepoutre A, Fonteneau L, Baudon C, Halftermeyer-Zhou F, Y LES, Levy-Bruhl D. Seroprevalence of cytomegalovirus infection in France in 2010. Epidemiol Infect. 2017;145(7):1471-8.
39. Cannon MJ. Congenital cytomegalovirus (CMV) epidemiology and awareness. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2009;46 Suppl 4:S6-10.
40. Mollers M, Vossen JM, Scherpenisse M, van der Klis FR, Meijer CJ, de Melker HE. Review: current knowledge on the role of HPV antibodies after natural infection and vaccination: implications for monitoring an HPV vaccination programme. Journal of medical virology. 2013;85(8):1379-85.
41. Introcaso CE, Dunne EF, Hariri S, Panicker G, Unger ER, Markowitz LE. Prevaccine era human papillomavirus types 6, 11, 16 and 18 seropositivity in the U.S.A., National Health and Nutrition Examination Surveys, 2003-2006. Sexually transmitted infections. 2014;90(6):505-8.

42. Pinto LA, Dillner J, Beddows S, Unger ER. Immunogenicity of HPV prophylactic vaccines: Serology assays and their use in HPV vaccine evaluation and development. Vaccine. 2018;36(32 Pt A):4792-9.
43. Ferguson M, Heath A, Johnes S, Pagliusi S, Dillner J, participants Obotcs. Results of the first WHO international collaborative study on the standardization of the detection of antibodies to human papillomaviruses. International Journal of Cancer. 2006;118(6):1508-14.
44. Michael KM, Waterboer T, Sehr P, Rother A, Reidel U, Boeing H, Bravo IG, Schlehofer J, Gartner BC, Pawlita M. Seroprevalence of 34 human papillomavirus types in the German general population. PLoS Pathog. 2008;4(6):e1000091.
45. Rahman S, Pierce Campbell CM, Rollison DE, Wang W, Waterboer T, Michel A, Pawlita M, Villa LL, Lazcano Ponce E, Borenstein AR, Giuliano AR. Seroprevalence and Associated Factors of 9-Valent Human Papillomavirus (HPV) Types among Men in the Multinational HIM Study. PloS one. 2016;11(11):e0167173.
46. Wilson L, Pawlita M, Castle PE, Waterboer T, Sahasrabuddhe V, Gravitt PE, Schiffman M, Wentzensen N. Seroprevalence of 8 oncogenic human papillomavirus genotypes and acquired immunity against reinfection. The Journal of infectious diseases. 2014;210(3):448-55.
47. Delere Y, Remschmidt C, Leuschner J, Schuster M, Fesenfeld M, Schneider A, Wichmann O, Kaufmann AM. Human Papillomavirus prevalence and probable first effects of vaccination in 20 to 25 year-old women in Germany: a population-based cross-sectional study via home-based self-sampling. BMC infectious diseases. 2014;14:87.
48. Iftner T, Eberle S, Iftner A, Holz B, Banik N, Quint W, Straube AN. Prevalence of low-risk and high-risk types of human papillomavirus and other risk factors for HPV infection in Germany within different age groups in women up to 30 years of age: an epidemiological observational study. Journal of medical virology. 2010;82(11):1928-39.
49. Petry KU, Luyten A, Justus A, Iftner A, Strehlke S, Reinecke-Luthge A, Grunwald E, Schulze-Rath R, Iftner T. Prevalence of high-risk HPV types and associated genital diseases in women born in 1988/89 or 1983/84--results of WOLVES, a population-based epidemiological study in Wolfsburg, Germany. BMC infectious diseases. 2013;13:135.
50. Rieck TFM WO, Siedler, A,. Impfquoten von Kinderschutzimpfungen in Deutschland – aktuelle Ergebnisse aus der RKI-Impfsurveillance. Epidemiol Bull. 2020;32/33:9–27.
51. Alfaro-Murillo JA, Townsend JP, Galvani AP. Optimizing age of cytomegalovirus screening and vaccination to avert congenital disease in the US. Vaccine. 2016;34(2):225-9.

2. EIDESSTATTLICHE VERSICHERUNG

„Ich, Anna Dorothea Loenenbach, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Seroepidemiologie und bevölkerungsbezogene Infektions- und Erkrankungsrisiken von Humanen Papillomviren (HPV) und Zytomegalievirus (CMV) anhand von Seren der zwei repräsentativen Gesundheitssurveys 'Kinder- und Jugendgesundheitssurvey (KiGGS-Basiserhebung)' und 'Survey zur Gesundheit von Erwachsenen (BGS98)'; Seroepidemiology and population-related infection and disease risks of human papillo-maviruses (HPV) using sera from two representative health surveys: German Health Survey for Children and Adolescents (KiGGS)' and 'The German National Health Inter-view and Examination Survey 1998 (GNHIES98)' selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Erstbetreuer, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst."

Datum	Unterschrift

3. ANTEILSERKLÄRUNG AN DEN ERFOLGTEN PUBLIKATIONEN

Anna Loenenbach hatte folgenden Anteil an den folgenden Publikationen:

PUBLIKATION 1

Lachmann R, Loenenbach A, Waterboer T, Brenner N, Pawlita M, Michel A, Thamm M, Poethko-Müller C, Wichmann O, Wiese-Posselt M. Cytomegalovirus (CMV) seroprevalence in the adult population of Germany, PLoS One, 2018.

Anteil an der Publikation:

- Hauptverantwortlich für die Datenbereinigung und Zusammenführung der epidemiologischen und serologischen Daten der Studie
- Mitverantwortlich, neben Erstautorin, für die Analyse der Daten
- Inhaltliche Prüfung aller Tabellen und Grafiken, die von Erstautorin erstellt wurden
- Interpretation der Ergebnisse in Zusammenarbeit mit den Koautoren*innen
- Revidieren des Manuskripts

PUBLIKATION 2

Loenenbach AD, Poethko-Müller C, Pawlita M, Thamm M, Harder T, Waterboer T, Schröter J, Deleré Y, Wichmann O, Wiese-Posselt M. Mucosal and cutaneous Human Papillomavirus seroprevalence among adults in the prevaccine era in Germany - Results from a nationwide population-based survey, Int J Infect Dis, 2019

Anteil an der Publikation:

- Hauptverantwortlich für die Datenbereinigung und Zusammenführung der epidemiologischen und serologischen Daten der Studie
- Verantwortlich für die Planung und Umsetzung des Studiendesigns in Zusammenarbeit und Absprache mit den Betreuenden
- Eigenständige Durchführung der Literaturrecherche und Auswahl der relevanten Literatur
- Eigenständige Analyse der Studiendaten unter der Berücksichtigung der Anmerkungen der Koautor*innen
- Eigenständige Erstellung aller Tabellen und Grafiken unter der Berücksichtigung der Anmerkungen der Koautor*innen
- Federführung bei Diskussion und Interpretation der Ergebnisse in Zusammenarbeit mit den Koautor*innen
- Eigenständige Konzeption, Erstellung sowie Finalisierung der Publikation unter der Berücksichtigung der Anmerkungen der Koautor*innen

PUBLIKATION 3

Loenenbach A, Pawlita, M., Waterboer, T., Poethko-Müller, C., Thamm, M., Harder, T., Wichmann, O., Wiese-Posselt, M. Seroprevalence of mucosal and cutaneous Human Papillomavirus (HPV) types among children and adolescents in the general population in Germany. BMC Inf Dis, 2022.

Anteil an der Publikation:

- Hauptverantwortlich für die Datenbereinigung und Zusammenführung der epidemiologischen und serologischen Daten der Studie
- Mitarbeit in der Bewertung und Einordnung der quantitativen Laborergebnisse
- Verantwortlich für die Planung und Umsetzung des Studiendesigns in Zusammenarbeit und Absprache mit den Betreuenden
- Eigenständige Durchführung der Literaturrecherche und Auswahl der relevanten Literatur
- Eigenständige Analyse der Studiendaten unter Berücksichtigung der Anmerkungen der Koautor*innen
- Eigenständige Erstellung aller Tabellen und Grafiken unter Berücksichtigung der Anmerkungen der Koautor*innen
- Federführung bei Diskussion und Interpretation der Ergebnisse in Zusammenarbeit mit den Koautor*innen
- Eigenständige Konzeption, Erstellung sowie Finalisierung der Publikation unter der Berücksichtigung der Anmerkungen der Koautor*innen

_____

Unterschrift, Datum und Stempel des erstbetreuenden Hochschullehrers

_____

Unterschrift der Doktorandin

5. ORIGINALARBEITEN ALS PROMOTIONSLEISTUNG

5.1. PUBLIKATION 1

Lachmann, R., Loenenbach, A., Waterboer, T., Brenner, N., Pawlita, M., Michel, A., Thamm, M., Poethko-Muller, C., Wichmann, O. and Wiese-Posselt, M. Cytomegalovirus (CMV) seroprevalence in the adult population of Germany. PLoS One, 2018. 13(7): p. e0200267. Journal Impact Factor: 2,806; Journal Citation Reports; Jahr „2016"; Ausgewählte Kategorie „Multidisciplinary Sciences".

Journal Data Filtered By: **Selected JCR Year: 2016** Selected Editions: SCIE,SSCI
Selected Categories: **"MULTIDISCIPLINARY SCIENCES"** Selected Category Scheme: WoS

Gesamtanzahl: 64 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NATURE	671,254	40.137	1.433990
2	SCIENCE	606,635	37.205	1.159250
3	Nature Communications	123,958	12.124	0.722290
4	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	620,027	9.661	1.236860
5	National Science Review	512	8.843	0.002740
6	GigaScience	1,145	6.871	0.007590
7	Scientific Data	720	4.836	0.004690
8	Annals of the New York Academy of Sciences	44,545	4.706	0.039810
9	COMPLEXITY	1,429	4.621	0.002090
10	Scientific Reports	101,255	4.259	0.387610
11	Science Bulletin	1,087	4.000	0.003100
12	Journal of the Royal Society Interface	10,469	3.579	0.031990
13	Research Synthesis Methods	850	3.018	0.004300
14	PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A-MATHEMATICAL PHYSICAL AND ENGINEERING SCIENCES	16,362	2.970	0.031980
15	PLoS One	508,248	2.806	1.924690
16	PROCEEDINGS OF THE JAPAN ACADEMY SERIES B-PHYSICAL AND BIOLOGICAL SCIENCES	1,162	2.324	0.002390
17	Royal Society Open Science	864	2.243	0.003380
18	SCIENCE AND ENGINEERING ETHICS	1,050	2.229	0.002780
19	NATURWISSENSCHAFTEN	6,601	2.221	0.004320
20	PeerJ	3,993	2.177	0.017790
21	PROCEEDINGS OF THE ROYAL SOCIETY A-MATHEMATICAL PHYSICAL AND ENGINEERING SCIENCES	16,771	2.146	0.016750
22	CHINESE SCIENCE BULLETIN	10,996	1.649	0.016680
23	Proceedings of the Romanian Academy Series A-Mathematics Physics Technical Sciences Information Science	334	1.623	0.000850
24	FRACTALS-COMPLEX GEOMETRY PATTERNS AND SCALING IN NATURE AND SOCIETY	887	1.540	0.000890

PLOS ONE

RESEARCH ARTICLE

Cytomegalovirus (CMV) seroprevalence in the adult population of Germany

Raskit Lachmann[1,2,3]*, Anna Loenenbach[1,4], Tim Waterboer[5], Nicole Brenner[5], Michael Pawlita[5], Angelika Michel[5], Michael Thamm[6], Christina Poethko-Müller[6], Ole Wichmann[1], Miriam Wiese-Posselt[1]

1 Immunization Unit, Robert Koch-Institute, Berlin, Germany, **2** Postgraduate Training for Applied Epidemiology, Robert Koch-Institute, Berlin, Germany, **3** European Programme for Intervention Epidemiology Training, ECDC, Stockholm, Sweden, **4** Charité – University Medicine Berlin, Berlin, Germany, **5** Division Molecular Diagnostics of Oncogenic infections, Infection, inflammation and Cancer Program, German Cancer Research Center (DKFZ), Heidelberg, Germany, **6** Department of Epidemiology and Health Reporting, Robert Koch-Institute, Berlin, Germany

* LachmannR@rki.de

Citation: Lachmann R, Loenenbach A, Waterboer T, Brenner N, Pawlita M, Michel A, et al. (2018) Cytomegalovirus (CMV) seroprevalence in the adult population of Germany. PLoS ONE 13(7): e0200267. https://doi.org/10.1371/journal.pone.0200267

Editor: Michael Nevels, University of St Andrews, UNITED KINGDOM

Received: January 17, 2018

Accepted: June 23, 2018

Published: July 25, 2018

Data Availability Statement: The authors confirm that some access restrictions apply to the data underlying the findings. The data from the GNHIES98 study cannot be made publicly available because informed consent from study participants did not cover public deposition of data. However, the minimal data set underlying the findings presented in this article is archived in the 'Health Monitoring' Research Data Centre at the Robert Koch Institute (RKI) and can be accessed by all interested researchers on site. The 'Health Monitoring' Research Data Centre is accredited by

Abstract

Background

Infection with cytomegalovirus (CMV) remains asymptomatic in most immunocompetent hosts, but is the leading cause of congenital viral infection worldwide and can be life-threatening in immunocompromised individuals. We aimed to assess CMV seroprevalence in a nationally representative sample of adults in Germany and to identify sociodemographic factors associated with CMV seropositivity.

Methods

Blood samples from 6552 participants (18–79 years) of the "German National Health Interview and Examination Survey 1998", a population-based sample of the adult population in Germany, were tested for the presence of CMV antibodies using an Ig-multiplex assay. Weighted seroprevalence was calculated and weighted binomial regression was used to identify factors associated with CMV seropositivity.

Results

Overall CMV seroprevalence was 56.7% (95%CI: 54.8–58.7%), with a higher seroprevalence in women (62.3%) than in men (51.0%). Seroprevalence increased with age: from 31.8% to 63.7% in men and from 44.1% to 77.6% in women when comparing the 18–29 with the 70–79 year age-group, respectively. CMV seroprevalence in women of childbearing age (18–45 years) was 51.7%. Factors significantly associated with CMV seropositivity were age, country of birth, smoking status, education, living in northern Germany and number of household members. In addition, having attended child care was associated with seropositivity in men, and number of siblings and living in East Germany in women.

the German Data Forum according to uniform and transparent standards. On-site access to the minimal data set is possible at the Secure Data Center of the RKI´s 'Health Monitoring' Research Data Centre, which is located at General-Pape-Straße 64 in Berlin, Germany. Requests should be submitted to Dr. Ronny Kuhnert at the Robert Koch Institute, 'Health Monitoring' Research Data Centre, General-Pape-Straße 64, 12101 Berlin, Germany (e-mail: fdz@rki.de). The data used in this study were generated by the Robert Koch Institute and can be accessed by others in the way described above. The data are for data protection reasons only available on site. The authors of this study did not have any special access privileges.

Funding: The German National Health Interview and Examination Survey 1998 was funded by the German Ministry of Health, the German Ministry of Education and Research, and the Robert Koch Institute (Berlin, Germany). Laboratory testing for CMV-specific Ig by multiplex assay was funded by the German Ministry of Health and the Robert Koch Institute (Berlin, Germany), and in-house funding from the Molecular Diagnostics of Oncogenic Infections Division at the German Cancer Research Center (DKFZ, Heidelberg).

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: CI, Confidence Interval; CMV, Cytomegalovirus; DEGS, German Health Interview and Examination Survey for Adults; DKFZ, German Cancer Research Center; GNHIES98, German National Health Interview and Examination Survey 1998; Ig, Immunoglobulin; No, Number; pp150, Phosphoprotein 150; pp28, Phosphoprotein 28; pp52, Phosphoprotein 52; pp65, Phosphoprotein 65; PR, Prevalence ratio; Ref, Reference; RKI, Robert Koch-Institute.

Conclusion

Our results indicate that half the women of childbearing age were susceptible for primary CMV infection during pregnancy. CMV screening during pregnancy and informing seronegative women about CMV risk reduction measures could prevent congenital CMV infections with its serious consequences.

Background

Cytomegalovirus (CMV) is a human herpesvirus which is prevalent worldwide with an estimated seroprevalence of 45% to 100% in the general population [1]. After primary infection the virus remains latent. Transmission can occur through contact with CMV-infected body fluids both during primary infection or episodes of reactivation from latency. CMV infections are usually asymptomatic in immunocompetent hosts but can cause life-threatening complications in immunocompromised individuals [2]. CMV infection is a major hazard in patients with AIDS and other immune disorders, transplant recipients, individuals admitted to intensive-care units, and to some extent in elderly people. However, the highest disease burden is due to congenital CMV infection [2–4]. Worldwide, congenital CMV infection is the leading cause of neurological damage in children and is associated with growth retardation, hearing loss, permanent disabilities and microcephaly [5, 6].

Despite this considerable public health burden, few women are aware of congenital CMV infection [7–9]. Educating women about CMV transmission and preventive hygiene behaviour can significantly reduce primary CMV infections during pregnancy and thereby congenital CMV infections [10–14]. A vaccine would be necessary to significantly and permanently reduce congenital (and other) CMV infections. To date, there is no licensed vaccine available that protects against CMV. However, several vaccine candidates are currently being tested in clinical trials [15–17]. A vaccine against CMV was classified as a top priority by "The National Vaccine Advisory Committee" in the US in 2004, based on the estimation that the disease burden of congenital CMV infection is as high as the disease burden due to congenital rubella before the introduction of rubella vaccinations [18, 19]. Representative epidemiological data on the CMV susceptibility of the population are essential for decision making in the fields of public health and primary prevention through immunization. Since there has been no population-based CMV-specific Ig seroprevalence data available for German adults, the aims of this study were to estimate CMV seroprevalence in the adult population in Germany and to identify socio-demographic and lifestyle factors that are potentially associated with CMV seropositivity.

Methods

Study population

The German National Health Interview and Examination Survey 1998 (GNHIES98) was the first nationwide representative survey on the health status of Germany's adult population after the German reunification in 1990. A nationwide two-stage clustered sample design with a selection of study points was used. The sampling of the 120 study points was done with a probability proportional to community size and federal state. Persons aged 18–79 years stratified by sex and age-group from the local population registers were subsequently sampled [20]. The net sample of the GNHIES98 consisted of 7124 persons (response: 61%) from 120 study points.

Subjects were eligible if they were familiar with the German language and were able to complete the questionnaires.

Although there was no law or regulation on Ethic Committees in Germany at the time of the conduct of the study, the study, including the analysis of the CMV-specific Ig data, was approved by the Board of the Federal Commissioner for Data Protection Berlin, Germany. The study was conducted according to the Federal and State Commissioners for Data Protection guidelines. Informed written consent and assent were obtained from all participants and all data were fully pseudomized before analysis.

Survey methods

In total, 7124 participants were examined at local study centers and blood samples were taken from a total of 6757 individuals (94.8%). For the study on CMV-specific Ig prevalence, blood samples of 6552 (92.0%) participants were available. Information on socio-demographic and lifestyle variables were obtained by standardized self-administered questionnaires. Place of residence was categorized into North, Middle and South Germany (Region I) as well as into former East and West Germany (Region II). Country of birth was categorized as Germany or other than Germany. Education was categorized into three levels (low, medium, high) according to the "International Standard Classification of Education". Smoking status was categorized into never smoking, former smoking and current smoking. As a proxy for the number of children, the number of people under the age of 18 currently living in the household was used, since there were no data on gravidity or parity available. As a proxy for siblings, the number of children grown up with was used.

Laboratory methods

Blood samples from the GNHIES98, which were stored at the Robert Koch Institute in Berlin at -70˚C, were shipped to the German Cancer Research Center (DKFZ) in Heidelberg, Germany. Here, a multiplex serology assay was used to detect CMV-specific IgG, IgM and IgA simultaneously. Antigen preparation and test methods were previously described elsewhere [21, 22]. Briefly, plasma samples diluted 1:1000 were tested for antibodies against 4 human CMV proteins (pp28, pp52, pp65 and pp150) bacterially expressed as glutathione *S*-transferase (GST) fusion proteins. The multiplex antibody detection approach was based on a GST capture immunosorbent assay in combination with fluorescent bead technology (Luminex Corporation, Austin, Texas) [22, 23]. The seropositivity threshold for each protein was set at a median fluorescence intensity (MFI) of 150 units and an individual was defined as CMV seropositive if two or more CMV-specific proteins were above the threshold. A validation of the CMV-specific multiplex assay was performed against Enzygnost anti-CMV/IgG and showed excellent sensitivity and specificity values (Brenner et al. in preparation).

Data analysis

In order to assure that estimates derived from the GNHIES98 study are representative at the national level, survey weights were applied throughout the statistical analyses which accounted for the stratified and clustered sample design of the survey [20]. The survey weight takes into account the region, sex, and age distribution of the population of Germany in the year of the survey (1998). To ensure representativeness, the subpopulation with available data for CMV serostatus was compared to the total GNHIES population.

Analyses were conducted in a stratified dataset, in which men and women were analysed separately to account for gender differences. Univariate analysis was used to identify associations between sociodemographic factors and CMV seropositivity. Factors that were identified

as possible influencing factors on CMV seropositivity in the literature and with a p-value <0.20 in the univariate analysis were included in the multivariable weighted binomial regression model. Interactions between factors were taken into consideration in the multivariable model. The final multivariable model included all factors that were associated with CMV seropositivity at a $p<0.05$ level in a forward stepwise selection approach. Results were expressed as weighted crude and adjusted prevalence ratios (PRs) with their 95% confidence intervals (95% CI). All analyses were done with STATA14.

Results

CMV seroprevalence in the adult population of Germany

The results are based on data from 6552 participants. Characteristics of the study population are shown in Table 1. The study population was representative of the adult population in Germany with an age range from 18 to 79 years and 51.5% of the participants being female. An analysis showed no significant differences regarding sociodemographic factors between the study population and the total GNHIES98 population (N = 7124).

Overall CMV seroprevalence in the adult population of Germany was estimated to be 56.7% (95% CI: 54.8–58.7%). In men, CMV seroprevalence was 51.0% (95% CI: 48.7–53.3%) and in women 62.3% (95% CI: 59.8–64.6%) Seroprevalence increased with age (Fig 1). In men, seroprevalence increased from 31.8% (95%CI: 27.3–36.8%) to 63.7% (95% CI: 55.6–71.1%) when comparing 18 to 29 with 70 to 79 years old individuals. In women, seroprevalence increased from 44.1% (95% CI: 38.8–49.5%) in 18 to 29 years old women to 77.6% (95% CI: 70.8–83.2%) in 70 to 79 years old women (Fig 1). In all age groups, CMV seroprevalence was higher in women than in men. Estimated CMV seroprevalence was higher in North Germany (Men: 52.4%, 95% CI: 48.4–56.5%; Women: 65.6% 95% CI: 61.4–69.6%) than in South Germany (Men: 47.1%, 95% CI: 43.3–51.0%; Women: 57.1% 95% CI: 52.8–61.3%). Total CMV seroprevalence in women of childbearing age (18–45 years) was 51.7% (95% CI: 47.8–54.3%). The study population included 34 women pregnant at the time of study participation. Of these, 13 (34%) were CMV seropositive.

Factors associated with CMV seropositivity

The weighted crude and adjusted PR for men and women can be found in Table 2. In the multivariable model mutually adjusted for all other variables, the following factors were associated with CMV seropositivity in Germany in both, men and women: age (PR men: 1.02; women: 1.02), country of birth other than Germany (PR men: 1.76; women: 1.52;), current smoking (PR men: 1.11; women: 1.11), living in northern Germany (PR men: 1.15; women: 1.11), the number of household members under the age of 18 years (PR men: 1.09; women: 1.05;), and the level of education (PR men: 0.82; women: 0.90) (Table 2). Some factors were only associated with CMV seropositivity either in men or in women: attended child care during childhood (PR 0.91) was negatively associated with CMV seropositivity in men only, whereas in women, the number of siblings grown up with (PR 1.01) and living in East Germany (PR 1.14) were positively associated with CMV seropositivity. No significant terms of interaction between variables were identified. Residence in urban or rural regions and working with children (e.g. teacher, working in a kindergarten) was not associated with seropositivity in men or women, neither in uni- nor in multivariable analysis. Some variables that have been shown to be associated with CMV seropositivity in other studies, such as the number of sexual partners or income (and thereby socioeconomic status) were not included in this analysis because these variables were only available for less than 60% of the participants. The number of pregnant

Table 1. Study population characteristics, CMV seroprevalence study, GNHIES98, Germany (n = 6552 participants).

Variables		N	%
Total		6552	100
Age in years	17–29	1166	17.8
	30–39	1450	22.1
	40–49	1226	18.7
	50–59	1270	19.4
	60–69	940	14.4
	70–79	500	7.6
Sex	Male	3172	48.4
	Female	3380	51.6
Country of birth	German	5769	88.0
	Other	606	9.3
	Missing	177	2.7
Smoking status	Never smoking	2907	44.4
	Previous smoking	1395	21.3
	Current smoking	2097	21
	Missing	153	2.3
Region I in Germany	North	1679	25.6
	Middle	3008	45.9
	South	1865	28.5
Region II in Germany	East	2232	34.1
	West	4320	65.9
Education	Low	1121	17.1
	Middle	3668	56
	High	1587	24.2
	Missing	176	2.7
Attended child care	Yes	3224	49.2
	No	3140	47.9
	Missing	188	2.9
No of household members <18 yrs	0	4136	63.1
	> = 1	2233	34.1
	Missing	183	2.8
No of children grown up with	0	926	14.1
	> = 1	5442	83.1
	Missing	184	2.8
CMV serostatus	Negative	2867	43.3
	Positive	3685	56.7

https://doi.org/10.1371/journal.pone.0200267.t001

women (N = 34, age 20–41 years, median age 32 years) in this study was too small for further analysis.

Discussion

This is the first nationwide, representative CMV serosurvey in the adult population of Germany. Although these sera were collected in 1998, this population based CMV seroprevalence data are an important source for epidemiological modelling and they will serve as baseline data of longitudinal surveys in the future. In this study, 51% of men and 62% of women were positive for CMV-specific Ig; these data are comparable to seroprevalence data from France

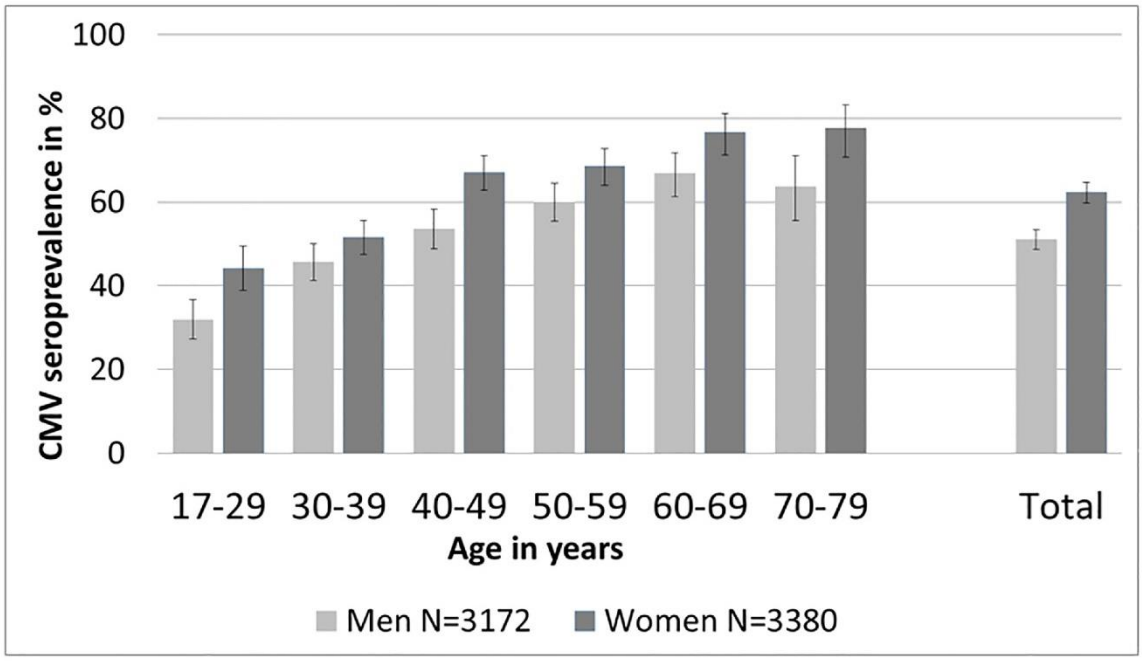

Fig 1. Estimated CMV seroprevalence (in percent) and 95% CI in adults in Germany, by age group and sex. In addition, overall seroprevalence and 95% CI by sex (men = light grey, women = dark grey) are shown on the right. Germany, n = 6552, sera collected 1998–1999.

https://doi.org/10.1371/journal.pone.0200267.g001

Table 2. Results of univariable (crude PR) and multivariable model (adjusted PR) with CMV seropositivity as the dependent variable; data set stratified by gender; Germany (sera collected 1998–1999, n = 6552).

Variables		Men		Women	
		Crude PR (95%CI)	Fully adjusted PR (95%CI)*	Crude PR (95%CI)	Fully adjusted PR (95%CI)*
Age in years Country of Birth		1.01 (1.01–1.02)	1.02 (1.01–1.02)	1.01 (1.01–1.01)	1.02 (1.01–1.02)
	Germany	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	Other	1.85 (1.70–2.02)	1.76 (1.62–1.92)	1.50 (1.41–1.60)	1.52 (1.41–1.63)
Smoking status	Non-smoking	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	Previous smoking	1.27 (1.15–1.42)	1.10 (1.00–1.21)	0.92 (0.84–1.01)	1.02 (0.94–1.11)
	Smoking	1.11 (1.00–1.23)	1.11 (1.01–1.21)	0.95 (0.88–1.02)	1.12 (1.04–1.20)
Region I in Germany	South	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	Middle	1.13 (1.02–1.25)	1.15 (1.05–1.27)	1.13 (1.03–1.23)	1.08(0.98–1.19)
	North	1.11 (1.00–1.24)	1.16 (1.04–1.29)	1.15 (1.04–1.27)	1.13 (1.03–1.24)
No of household members <18 yrs		1.03 (0.99–1.07)	1.07 (1.03–1.12)	0.96 (0.92–1.00)	1.05 (1.01–1.09)
Education	Low	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	Middle	0.74 (0.67–0.81)	0.85 (0.77–0.93)	0.78 (0.73–0.83)	0.92 (0.86–0.98)
	High	0.75 (0.66–0.84)	0.82 (0.72–0.92)	0.77 (0.70–0.85)	0.90 (0.82–1.00)
Attended child care	No	1 (Ref)	1 (Ref)	1 (Ref)	ns#
	Yes	0.71 (0.65–0.78)	0.91 (0.83–1.00)	0.81 (0.75–0.87)	
Region II in Germany	West	1 (Ref)	ns#	1 (Ref)	1 (Ref)
	East	1.02 (0.93–1.11)		1.15 (1.04–1.19)	1.15 (1.08–1.23)
No of children grown up with		1.07 (1.05–1.09)	ns#	1.02 (1.01–1.03)	1.01 (1.00–1.02)

* Mutually adjusted for all other variables in the model,

ns = Variables were not significantly associated with CMV seroprevalence in the final model and therefore excluded

https://doi.org/10.1371/journal.pone.0200267.t002

and the Netherlands [24, 25]. In contrast, populations in Portugal (77%), Sweden (83%) and Croatia (77%) seem to have slightly higher CMV seroprevalence [26–28].

In our study, age and country of birth were the most prominent independent factors associated with CMV seropositivity as it was shown in studies from other countries [1, 29, 30]. The increase of CMV seroprevalence with age is well known and results from cumulative exposure to CMV throughout life. The association between country of birth and CMV seroprevalence has been shown previously [1, 25, 31, 32]. Seroprevalence differences between countries may be explained by differences in the prevalence of key exposures related to CMV transmission: breastfeeding frequency and duration, crowding, childcare arrangements and sexual behaviours [1].

CMV seroprevalence is usually higher in women than in men, which indicates that the exposure to CMV might be partially different between genders. In most publications investigating factors associated with CMV seropositivity, gender is being adjusted for but not analysed separately. Using the stratified approach for gender the results shown here indicate that factors associated with CMV seropositivity indeed varied partially between men and women. The number of siblings was associated with CMV seropositivity only in women and not in men. One reason may be different playing behaviours and traditional role patterns, with women having been more involved in caring for their siblings in childhood and therefore more exposed to CMV shed by young children. In line with the high risk of CMV transmission from young children, the number of household members under the age of 18 years was associated with CMV seropositivity. Since the number of children raised was not available, the variable "number of household members under the age of 18 years" was used as a proxy. However, this proxy probably underestimated the real number of raised children. Young children constitute a well-known source of CMV because they often excrete large amounts of virus in their saliva and urine for a long time and therefore attending childcare is usually associated with higher CMV seroprevalence [30, 32, 33]. It is unclear, why in our study having attended childcare was not associated with CMV seropositivity in women and was associated with lower CMV seropositivity in men. In the past, child care settings differed in East and West Germany and also changed over time hindering interpretation. As in other studies, higher education was inversely associated with CMV seropositivity in this study [24, 25, 32, 34, 35]. Moreover it is known that smoking has an influence on the immune system and thereby on viral infections [36]. As in our study, smoking has also been shown to be associated with CMV seropositivity previously but it is still unclear if smoking has a direct effect on CMV infection or if it is a proxy for other lifestyle factors [37, 38]. Our results indicate that there were significant regional differences in the CMV seroprevalence in Germany as has been shown for other countries [25, 26, 39]. More lifestyle and behavioural data would be necessary to investigate what causes these regional differences.

In our study 51.7% of women of childbearing age were estimated to be CMV seropositive; thus, around half of women aged 18 to 45 years were susceptible for primary CMV infection. However, congenital CMV infections can occur both as a result of primary infection and after a reinfection or reactivation of latent CMV infection. A meta-analysis of Kenneson et al. estimated that 32% of primary infections and 1.4% of recurrent infections during pregnancy lead to congenital infection [40]. Due to high CMV seroprevalence globally, seropositive mothers account for the majority of CMV-induced permanent disabilities in children, even though the risk for congenital infection is higher in primary infections [40]. However, due to the relatively low seroprevalence, in Germany primary CMV infections during pregnancy are epidemiologically more important than reinfections and reactivation in CMV-seropositive pregnant women [41]. In a recent literature review Buxmann et al. estimated that annually 700–1400 children in Germany suffer from severe permanent disabilities due to congenital CMV

[41]. Primary CMV infection (and probably reinfections) can be reduced significantly if women are educated about CMV transmission and preventive hygiene behaviours [10–14]. Despite the high disease burden, few women are aware of the risk of congenital CMV infection and CMV screening is not part of routine antenatal test [7–9, 42, 43]. If informed about preventive measures, women showed positive attitudes toward CMV prevention behaviours and perceived them as feasible [8]. These CMV prevention behaviours include washing hands after exposure to young children's bodily fluids, not sharing food, cups, or other utensils with children, not putting a pacifier in the mouth after it had been in a child's mouth, and not kissing children on the lips [8, 14]. The results from this study suggest that many women of childbearing age are at risk of primary CMV infection and that there are no easily identifiable high-risk groups.

To date, there is no vaccine available that prevents primary or reactivation of CMV infection even though a vaccine would be the best chance to reduce the burden of CMV infection. However, several vaccine candidates are in clinical development, and a vaccine against CMV was classified as a top priority by "The National Vaccine Advisory Committee" in the US in 2004 which has triggered commercial interest [15–19]. In order to develop public health recommendations regarding the use of a CMV vaccine once available in the future, representative epidemiological data on the susceptibility of the population and the burden of CMV infection are essential. Since there are no population-based seroprevalence data for CMV antibodies available for Germany, the present study was conducted. Knowledge about population-based age-stratified CMV prevalence is necessary for the design of age-specific vaccination strategies [44]. Therefore population based surveys, such as the GNHIES98, provide useful seroprevalence data to be included in transmission models and to inform future vaccination strategies. Beyond the primary goal of reducing congenital CMV infection, the reduction in CMV transmission achieved by CMV vaccination could have further indirect benefits in terms of lowering CMV incidence in the immunocompromised and the elderly in an ageing population [44]. Meanwhile, CMV screening during pregnancy and educating women about CMV risk reduction measures could reduce congenital CMV infections with its serious consequences.

CMV seropositivity in our study was measured by GST-based multiplex serology assay which showed excellent sensitivity and specificity values in a validation study but may not be identical to estimates measured using other assays. The use of an assay which detects IgG, IgA and IgM simultaneously achieves high sensitivity but unfortunately it is not possible to analyse the different Ig-classes separately.

A major strength of this study was the use of a representative population-based sample to determine CMV seroprevalence. Because of the large sample size and the population-wide weighted sampling procedure the study also had sufficient statistical power to enable a reliable multivariable analysis of factors associated with CMV seropositivity. Even though a weighting factor was used in the analysis and a high response of 61% among eligible persons was achieved, some bias might be present since institutionalized persons and persons with inadequate German language skills were excluded. For this reason, the subpopulation of migrants in this study is not representative for migrants in Germany. In addition, for some factors, the individual status at the time of the survey may not reflect past exposure.

One important limitation is the age of the data used for this study. The sera were collected in 1998 and the CMV seroprevalence in the present population in Germany might have changed since then. Even though it can be assumed that CMV seroprevalence did not change substantially in the last 20 years (due to the long co-evolution between humans and human CMV [45]), further seroprevalence studies are necessary to confirm CMV seroprevalence in the present population in Germany. Due to changing circumstances (German reunification), lifestyle and behaviours (e.g. higher level of mobility of people moving around Germany,

higher rate of children visiting day-care facilities) might have changed substantially in the population of Germany over the last 20 years which might affect CMV seroprevalence as well. Especially the immigration of refugees in the recent years should be considered in future surveys. Studies in the US showed no changes in the CMV seroprevalence of the total population, whereas studies in pregnant women only showed decreasing seroprevalence in Japan and increasing CMV seroprevalence in Norway [39, 46–48]. Since the participants in GNHIES98 constitute the baseline cohort for health interviews and examinations that were conducted in 2008–2011, the results from this study could also provide an excellent baseline for a longitudinal serosurvey. Longitudinal analysis would be essential to investigate if CMV seroprevalence changed over the last 20 years and if so which factors were associated with it.

Conclusion

In conclusion, our study constitutes the first population-based seroprevalence data based on a large sample representative for the adult population living in Germany. These data indicate that a substantial proportion of women in childbearing age were susceptible to primary CMV infection. Further seroprevalence studies with more recent data are necessary to evaluate CMV seroprevalence in the German population and to better understand the epidemiology of CMV infection. As long as no effective vaccine is commercially available, the primary prevention measure should be educating women about CMV risk reduction measures.

Acknowledgments

We thank Ronny Kuhnert and other colleagues from the Department of Epidemiology and Health Reporting, RKI, Berlin, Germany for the data collection and data management. We also wish to thank all participants in this study.

Author Contributions

Conceptualization: Ole Wichmann, Miriam Wiese-Posselt.

Data curation: Tim Waterboer, Michael Thamm, Christina Poethko-Müller.

Formal analysis: Raskit Lachmann, Anna Loenenbach.

Funding acquisition: Ole Wichmann, Miriam Wiese-Posselt.

Methodology: Raskit Lachmann, Tim Waterboer, Nicole Brenner, Michael Pawlita, Angelika Michel, Christina Poethko-Müller.

Supervision: Miriam Wiese-Posselt.

Writing – original draft: Raskit Lachmann.

Writing – review & editing: Raskit Lachmann, Anna Loenenbach, Tim Waterboer, Michael Thamm, Christina Poethko-Müller, Miriam Wiese-Posselt.

References

1. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol. 2010; 20(4):202–13. https://doi.org/10.1002/rmv.655 PMID: 20564615.
2. Griffiths PD. Burden of disease associated with human cytomegalovirus and prospects for elimination by universal immunisation. Lancet Infect Dis. 2012; 12(10):790–8. https://doi.org/10.1016/S1473-3099(12)70197-4 PMID: 23017365.
3. Lancini D, Faddy HM, Flower R, Hogan C. Cytomegalovirus disease in immunocompetent adults. Med J Aust. 2014; 201(10):578–80. PMID: 25390262.

4. Rafailidis PI, Mourtzoukou EG, Varbobitis IC, Falagas ME. Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. Virol J. 2008; 5:47. https://doi.org/10.1186/1743-422X-5-47 PMID: 18371229.
5. Ludwig A, Hengel H. Epidemiological impact and disease burden of congenital cytomegalovirus infection in Europe. Euro Surveill. 2009; 14(9):26–32. PMID: 19317969.
6. Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev. 2013; 26(1):86–102. https://doi.org/10.1128/CMR.00062-12 PMID: 23297260.
7. Willame A, Blanchard-Rohner G, Combescure C, Irion O, Posfay-Barbe K, Martinez de Tejada B. Awareness of Cytomegalovirus Infection among Pregnant Women in Geneva, Switzerland: A Cross-sectional Study. Int J Environ Res Public Health. 2015; 12(12):15285–97. https://doi.org/10.3390/ijerph121214982 PMID: 26633451.
8. Thackeray R, Magnusson BM. Women's attitudes toward practicing cytomegalovirus prevention behaviors. Prev Med Rep. 2016; 4:517–24. https://doi.org/10.1016/j.pmedr.2016.09.008 PMID: 27747148.
9. Binda S, Pellegrinelli L, Terraneo M, Caserini A, Primache V, Bubba L, et al. What people know about congenital CMV: an analysis of a large heterogeneous population through a web-based survey. BMC Infect Dis. 2016; 16(1):513. https://doi.org/10.1186/s12879-016-1861-z PMID: 27671033.
10. Picone O, Vauloup-Fellous C, Cordier AG, Parent Du Chatelet I, Senat MV, Frydman R, et al. A 2-year study on cytomegalovirus infection during pregnancy in a French hospital. BJOG. 2009; 116(6):818–23. https://doi.org/10.1111/j.1471-0528.2009.02139.x PMID: 19432571.
11. Reichman O, Miskin I, Sharoni L, Eldar-Geva T, Goldberg D, Tsafrir A, et al. Preconception screening for cytomegalovirus: an effective preventive approach. Biomed Res Int. 2014; 2014:135416. https://doi.org/10.1155/2014/135416 PMID: 25013756.
12. Adler SP, Finney JW, Manganello AM, Best AM. Prevention of child-to-mother transmission of cytomegalovirus among pregnant women. J Pediatr. 2004; 145(4):485–91. https://doi.org/10.1016/j.jpeds.2004.05.041 PMID: 15480372.
13. Vauloup-Fellous C, Picone O, Cordier AG, Parent-du-Chatelet I, Senat MV, Frydman R, et al. Does hygiene counseling have an impact on the rate of CMV primary infection during pregnancy? Results of a 3-year prospective study in a French hospital. J Clin Virol. 2009; 46 Suppl 4:S49–53. https://doi.org/10.1016/j.jcv.2009.09.003 PMID: 19811947.
14. Revello MG, Tibaldi C, Masuelli G, Frisina V, Sacchi A, Furione M, et al. Prevention of Primary Cytomegalovirus Infection in Pregnancy. EBioMedicine. 2015; 2(9):1205–10. https://doi.org/10.1016/j.ebiom.2015.08.003 PMID: 26501119.
15. Smith LR, Wloch MK, Chaplin JA, Gerber M, Rolland AP. Clinical Development of a Cytomegalovirus DNA Vaccine: From Product Concept to Pivotal Phase 3 Trial. Vaccines (Basel). 2013; 1(4):398–414. https://doi.org/10.3390/vaccines1040398 PMID: 26344340.
16. Bernstein DI, Munoz FM, Callahan ST, Rupp R, Wootton SH, Edwards KM, et al. Safety and efficacy of a cytomegalovirus glycoprotein B (gB) vaccine in adolescent girls: A randomized clinical trial. Vaccine. 2016; 34(3):313–9. https://doi.org/10.1016/j.vaccine.2015.11.056 PMID: 26657184.
17. Pass RF, Zhang C, Evans A, Simpson T, Andrews W, Huang ML, et al. Vaccine prevention of maternal cytomegalovirus infection. N Engl J Med. 2009; 360(12):1191–9. https://doi.org/10.1056/NEJMoa0804749 PMID: 19297572.
18. Arvin AM, Fast P, Myers M, Plotkin S, Rabinovich R, National Vaccine Advisory C. Vaccine development to prevent cytomegalovirus disease: report from the National Vaccine Advisory Committee. Clin Infect Dis. 2004; 39(2):233–9. https://doi.org/10.1086/421999 PMID: 15307033.
19. Bernstein DI. Congenital Cytomegalovirus: a "Now" Problem-No Really, Now. Clin Vaccine Immunol. 2017; 24(1). https://doi.org/10.1128/CVI.00491-16 PMID: 27795304.
20. Thefeld W, Stolzenberg H, bellach B-M. Bundes-Gesundheitssurvey: Response, Zusammensetzung der Teilnehmer und Non-Responder-Analyse. 1999.
21. Michael KM, Waterboer T, Sehr P, Rother A, Reidel U, Boeing H, et al. Seroprevalence of 34 human papillomavirus types in the German general population. PLoS Pathog. 2008; 4(6):e1000091. https://doi.org/10.1371/journal.ppat.1000091 PMID: 18566657.
22. Waterboer T, Sehr P, Michael KM, Franceschi S, Nieland JD, Joos TO, et al. Multiplex human papillomavirus serology based on in situ-purified glutathione s-transferase fusion proteins. Clin Chem. 2005; 51(10):1845–53. https://doi.org/10.1373/clinchem.2005.052381 PMID: 16099939.
23. Waterboer T, Sehr P, Pawlita M. Suppression of non-specific binding in serological Luminex assays. J Immunol Methods. 2006; 309(1–2):200–4. https://doi.org/10.1016/j.jim.2005.11.008 PMID: 16406059.

24. Korndewal MJ, Mollema L, Tcherniaeva I, van der Klis F, Kroes AC, Oudesluys-Murphy AM, et al. Cytomegalovirus infection in the Netherlands: seroprevalence, risk factors, and implications. J Clin Virol. 2015; 63:53–8. https://doi.org/10.1016/j.jcv.2014.11.033 PMID: 25600606.

25. Antona D, Lepoutre A, Fonteneau L, Baudon C, Halftermeyer-Zhou F, Y LES, et al. Seroprevalence of cytomegalovirus infection in France in 2010. Epidemiol Infect. 2017:1–8. https://doi.org/10.1017/S0950268817000103 PMID: 28166842.

26. Lopo S, Vinagre E, Palminha P, Paixao MT, Nogueira P, Freitas MG. Seroprevalence to cytomegalovirus in the Portuguese population, 2002–2003. Euro Surveill. 2011; 16(25). PMID: 21722611.

27. Vilibic-Cavlek T, Kolaric B, Beader N, Vrtar I, Tabain I, Mlinaric-Galinovic G. Seroepidemiology of cytomegalovirus infections in Croatia. Wien Klin Wochenschr. 2016. https://doi.org/10.1007/s00508-016-1069-7 PMID: 27599701.

28. Olsson J, Kok E, Adolfsson R, Lovheim H, Elgh F. Herpes virus seroepidemiology in the adult Swedish population. Immun Ageing. 2017; 14:10. https://doi.org/10.1186/s12979-017-0093-4 PMID: 28491117.

29. Cannon MJ. Congenital cytomegalovirus (CMV) epidemiology and awareness. J Clin Virol. 2009; 46 Suppl 4:S6–10. https://doi.org/10.1016/j.jcv.2009.09.002 PMID: 19800841.

30. Hecker M, Qiu D, Marquardt K, Bein G, Hackstein H. Continuous cytomegalovirus seroconversion in a large group of healthy blood donors. Vox Sang. 2004; 86(1):41–4. PMID: 14984558.

31. Voigt S, Schaffrath Rosario A, Mankertz A. Cytomegalovirus Seroprevalence Among Children and Adolescents in Germany: Data From the German Health Interview and Examination Survey for Children and Adolescents (KiGGS), 2003–2006. Open Forum Infect Dis. 2016; 3(1):ofv193. https://doi.org/10.1093/ofid/ofv193 PMID: 26817022.

32. Staras SA, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1988–1994. Clin Infect Dis. 2006; 43(9):1143–51. https://doi.org/10.1086/508173 PMID: 17029132.

33. Hyde TB, Schmid DS, Cannon MJ. Cytomegalovirus seroconversion rates and risk factors: implications for congenital CMV. Rev Med Virol. 2010; 20(5):311–26. https://doi.org/10.1002/rmv.659 PMID: 20645278.

34. Basha J, Iwasenko JM, Robertson P, Craig ME, Rawlinson WD. Congenital cytomegalovirus infection is associated with high maternal socio-economic status and corresponding low maternal cytomegalovirus seropositivity. J Paediatr Child Health. 2014; 50(5):368–72. https://doi.org/10.1111/jpc.12502 PMID: 24593837.

35. Dowd JB, Aiello AE, Alley DE. Socioeconomic disparities in the seroprevalence of cytomegalovirus infection in the US population: NHANES III. Epidemiol Infect. 2009; 137(1):58–65. https://doi.org/10.1017/S0950268808000551 PMID: 18413004.

36. Qiu F, Liang CL, Liu H, Zeng YQ, Hou S, Huang S, et al. Impacts of cigarette smoking on immune responsiveness: Up and down or upside down? Oncotarget. 2017; 8(1):268–84. https://doi.org/10.18632/oncotarget.13613 PMID: 27902485.

37. Hamer M, Batty GD, Kivimaki M. Obesity, Metabolic Health, and History of Cytomegalovirus Infection in the General Population. J Clin Endocrinol Metab. 2016; 101(4):1680–5. https://doi.org/10.1210/jc.2015-4208 PMID: 26863425.

38. Pampel FC, Krueger PM, Denney JT. Socioeconomic Disparities in Health Behaviors. Annu Rev Sociol. 2010; 36:349–70. https://doi.org/10.1146/annurev.soc.012809.102529 PMID: 21909182.

39. Odland ML, Strand KM, Nordbo SA, Forsmo S, Austgulen R, Iversen AC. Changing patterns of cytomegalovirus seroprevalence among pregnant women in Norway between 1995 and 2009 examined in the Norwegian Mother and Child Cohort Study and two cohorts from Sor-Trondelag County: a cross-sectional study. BMJ Open. 2013; 3(9):e003066. https://doi.org/10.1136/bmjopen-2013-003066 PMID: 24078749.

40. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol. 2007; 17(4):253–76. https://doi.org/10.1002/rmv.535 PMID: 17579921.

41. Buxmann H, Hamprecht K, Meyer-Wittkopf M, Friese K. Zytomegalievirus-Primärinfektion in der Schwangerschaft. Dtsch Arztebl International. 2017; 114(4):45–52.

42. Modrow S, Buxmann, Enders, Gembruch, Goelz, Hamprecht, et al. Management der kongenitalen Zytomegalievirus-Infektion bei Neugeborenen. Frauenarzt. 2018; 59:394–402.

43. Deutsche Vereinigung zur Bekämpfung der Viruskrankheiten, Virologie Gf. Labordiagnostik schwangerschaftsrelevanter Virusinfektionen S2k-Leitlinie2014.

44. Alfaro-Murillo JA, Townsend JP, Galvani AP. Optimizing age of cytomegalovirus screening and vaccination to avert congenital disease in the US. Vaccine. 2016; 34(2):225–9. https://doi.org/10.1016/j.vaccine.2015.11.039 PMID: 26631416.

45. Loewendorf A, Benedict CA. Modulation of host innate and adaptive immune defenses by cytomegalovirus: timing is everything. J Intern Med. 2010; 267(5):483–501. https://doi.org/10.1111/j.1365-2796.2010.02220.x PMID: 20433576.

46. Marshall GS, Stout GG. Cytomegalovirus seroprevalence among women of childbearing age during a 10-year period. Am J Perinatol. 2005; 22(7):371–6. https://doi.org/10.1055/s-2005-872590 PMID: 16215924.

47. Bate SL, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988–2004. Clin Infect Dis. 2010; 50(11):1439–47. https://doi.org/10.1086/652438 PMID: 20426575.

48. Taniguchi K, Watanabe N, Sato A, Jwa SC, Suzuki T, Yamanobe Y, et al. Changes in cytomegalovirus seroprevalence in pregnant Japanese women-a 10-year single center study. J Clin Virol. 2014; 59(3):192–4. https://doi.org/10.1016/j.jcv.2013.12.013 PMID: 24468011.

5.2. PUBLIKATION 2

Loenenbach A, Poethko-Müller, C., Pawlita, M., Thamm, M., Harder, T., Waterboer, T., Deleré, Y., Wichmann, O., Wiese-Posselt, M. Mucosal and cutaneous Human Papillomavirus seroprevalence among adults in the prevaccine era in Germany - Results from a nationwide population-based survey. Int J Infect Dis. 2019 Mar 20;83:3-11. doi: 10.1016/j.ijid.2019.03.022. Journal Impact Factor: 3,202; Journal Citation Reports; Jahr „2017"; Ausgewählte Kategorie „Infectious Diseases".

Journal Data Filtered By: **Selected JCR Year: 2017** Selected Editions: SCIE,SSCI
Selected Categories: **"INFECTIOUS DISEASES"** Selected Category
Scheme: WoS
Gesamtanzahl: 88 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	LANCET INFECTIOUS DISEASES	20,494	25.148	0.067280
2	Lancet HIV	1,476	11.355	0.007950
3	CLINICAL INFECTIOUS DISEASES	61,618	9.117	0.120010
4	EMERGING INFECTIOUS DISEASES	29,657	7.422	0.057980
5	Eurosurveillance	8,482	7.127	0.031200
6	INFECTIOUS DISEASE CLINICS OF NORTH AMERICA	2,503	5.449	0.005170
7	CLINICAL MICROBIOLOGY AND INFECTION	15,983	5.394	0.039650
8	JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY	29,292	5.217	0.050730
9	JOURNAL OF INFECTIOUS DISEASES	45,662	5.186	0.075270
10	Journal of the International AIDS Society	3,638	5.131	0.013920
11	AIDS	20,578	4.914	0.038030
12	INTERNATIONAL JOURNAL OF HYGIENE AND ENVIRONMENTAL HEALTH	4,282	4.848	0.006360
13	Current HIV/AIDS Reports	1,490	4.710	0.004890
14	JOURNAL OF INFECTION	6,636	4.603	0.014730
15	Travel Medicine and Infectious Disease	1,230	4.450	0.003610
16	Current Opinion in HIV and AIDS	2,266	4.409	0.008060
17	ACS Infectious Diseases	749	4.325	0.003090
18	INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS	10,395	4.253	0.016630

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
19	JOURNAL OF VIRAL HEPATITIS	4,846	4.237	0.010070
20	JAIDS-JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES	14,668	4.116	0.033010
21	AIDS PATIENT CARE AND STDS	3,622	4.041	0.006760
22	Virulence	2,944	3.947	0.008450
23	CURRENT OPINION IN INFECTIOUS DISEASES	3,582	3.782	0.008230
24	Antimicrobial Resistance and Infection Control	820	3.568	0.003260
25	Transboundary and Emerging Diseases	2,441	3.504	0.005680
26	Infection and Drug Resistance	640	3.443	0.002160
27	Epidemics	576	3.364	0.002410
28	JOURNAL OF HOSPITAL INFECTION	7,523	3.354	0.010450
29	SEXUALLY TRANSMITTED INFECTIONS	4,769	3.346	0.009050
30	INFECTION AND IMMUNITY	46,798	3.256	0.034450
31	Open Forum Infectious Diseases	1,598	3.240	0.009070
32	INTERNATIONAL JOURNAL OF INFECTIOUS DISEASES	6,424	3.202	0.015340
33	INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY	10,374	3.084	0.019450
34	Influenza and Other Respiratory Viruses	1,589	2.954	0.006130
35	HIV MEDICINE	2,581	2.932	0.006230
36	MICROBES AND INFECTION	6,655	2.924	0.006120
37	Clinical and Vaccine Immunology	5,741	2.872	0.011440
38	MALARIA JOURNAL	12,743	2.845	0.029220
39	MEDICAL MYCOLOGY	4,078	2.799	0.005660
40	AIDS REVIEWS	651	2.775	0.001430

Selected JCR Year: 2017; Selected Categories: "INFECTIOUS DISEASES"

International Journal of Infectious Diseases 83 (2019) 3–11

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Mucosal and cutaneous Human Papillomavirus seroprevalence among adults in the prevaccine era in Germany — Results from a nationwide population-based survey

Anna D. Loenenbach[a,b,1,*], Christina Poethko-Müller[c], Michael Pawlita[d], Michael Thamm[c], Thomas Harder[a], Tim Waterboer[d], Juliane Schröter[d], Yvonne Deleré[a], Ole Wichmann[a], Miriam Wiese-Posselt[a]

[a] Department for Infectious Disease Epidemiology, Immunization Unit, Robert Koch-Institute, Berlin, Germany
[b] Charité — University Medicine Berlin, Berlin, Germany
[c] Department of Epidemiology and Health Monitoring, Robert Koch-Institute, Berlin, Germany
[d] Division of Molecular Diagnostics of Oncogenic Infections, German Cancer Research Center (DKFZ), Heidelberg, Germany

ARTICLE INFO

Article history:
Received 3 September 2018
Received in revised form 13 March 2019
Accepted 14 March 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Human papillomavirus
Prevalence
Serology
Vaccine
General population
Seroepidemiologic studies
Predictors
Germany

ABSTRACT

Background: Human Papillomavirus (HPV) vaccination of girls was introduced in Germany in 2007. However, data on the distribution of vaccine-relevant HPV types in the general population in Germany in the prevaccine era are limited.
Methods: Serum samples collected during the German National Health Interview and Examination Survey 1998 (GNHIES98), a nationally representative study including men and women aged 18–79 years, were tested for antibodies to 19 mucosal and cutaneous HPV types. Multivariable regression models were developed to identify associations between demographic and behavioral characteristics and HPV seropositivity.
Results: Of the 6517 serum samples tested, almost a quarter was seropositive for at least one of the nine HPV vaccine types with no clear age-pattern. HPV-6 and HPV-59 were the most common mucosal types, while HPV-1 and HPV-4 were the most common cutaneous HPV types. Factors independently associated with HPV-16 seroprevalence were seropositive to other sexually transmitted infections and lifetime number of sex partners, as well as urbanity (only among females).
Conclusions: Prevalence of naturally acquired antibodies to HPV types which can be prevented by vaccination is high in both sexes and all age groups. These data can serve as baseline estimates to evaluate the population-level impact of the current vaccination strategy.

Background

About 200 different mucosal and cutaneous Human Papillomavirus (HPV) types have been characterized (Van Doorslaer et al., 2017), but only a small fraction is classified as oncogenic by the International Agency for Research on Cancer (IARC) (International Agency on Research on Cancer (IARC), 2012). The so-called high-risk (HR) types are considered to be causative agents of various types of precancerous lesions and cancer in women and men (International Agency on Research on Cancer (IARC), 2012; Schiffman et al., 2007). This group includes HPV types 16 and 18 as well as e.g., 31, 33, 35, 45, 52, and 58. External benign genital warts are mainly caused by low risk (LR) types 6 and 11 (International Agency on Research on Cancer (IARC), 2012). Cutaneous HPV types of different genera are common on healthy

Abbreviations: aPR, adjusted prevalence ratio; CI, confidence interval; DKFZ, German Cancer Research Center; GNHIES98, German National Health Interview and Examination Survey 1998; HPV, human papillomavirus; HPV-LR, low risk HPV types: 6, 11; HPV-HR, high risk HPV types: 16, 18, 31, 33, 35, 39, 45, 52, 58, 59; HPV-cut, cutaneous HPV types: 1, 4, 8, 10, 38, 41, 49; HPV-muc, mucosal HPV types: 6, 11, 16, 18, 31, 33, 35, 39, 45, 52, 58, 59; HPV-2val, HPV types in the bivalent vaccine: 16, 18; HPV-4val, HPV types in the quadrivalent vaccine: 6, 11, 16, 18; HPV-9val, HPV types in the nonavalent vaccine: 6, 11, 16, 18, 31, 33, 45, 52, 58; PR, prevalence ratio; Ref, reference; RKI, Robert Koch-Institute; STI, sexually transmitted infections; STI+, seropositivity for at least one of the following sexually transmitted infections: Mycoplasma genitalium (Mg), Herpes simplex 2 (HS2), Chlamydia trachomatis (Ct).

* Corresponding author at: Robert Koch Institute, Department for Infectious Disease Epidemiology, Seestrasse 10, 13353 Berlin, Germany.
E-mail address: aloenenbach@gmail.com (A.D. Loenenbach).
[1] Present address: RIVM, National Institute for Public Health and the Environment, Centre for Infectious Disease Control Netherlands (CIb), 3720 BA Bilthoven, The Netherlands.

https://doi.org/10.1016/j.ijid.2019.03.022

skin (Antonsson et al., 2000). However, they are also found in several skin lesions such as benign skin warts (de Villiers et al., 2004; International Agency on Research on Cancer (IARC), 2012), and some types have been discussed to be involved in skin carcinogenesis (Hufbauer and Akgül, 2017).

HPV prevalence differs mainly by HPV type but also by anatomical infection site and age (Iftner et al., 2010). Genital mucosal HPV are common sexually transmitted pathogens, but most HPV-infected persons develop no visible signs or symptoms. The majority of genital HPV infections are cleared within 12–24 months (Trottier and Franco, 2006), and persistent HPV infections with particular HR types are associated with an increased risk of anogenital or oropharyngeal cancer (de Villiers et al., 2004; International Agency on Research on Cancer (IARC), 2012; Schiffman et al., 2009). DNA testing has become the reference standard for the detection of current HPV infections (Abreu et al., 2012). However, it is not an appropriate method to assess previous infections (Robbins et al., 2014). Testing for HPV-specific antibodies provides information about past HPV exposure (Robbins et al., 2014; Tiggelaar et al., 2012). Therefore, HPV serology has been established as an important method for population-based studies focusing on type-specific cumulative lifetime exposure to HPV.

In Germany, HPV vaccination of girls has been introduced in 2007. Only limited data are available on the prevalence of HPV HR and LR types in the adult population of Germany (Michael et al., 2008). Previous studies were mainly performed in highly selected populations and focused on DNA prevalence in young women (Delere et al., 2014; Hauck et al., 2015; Iftner et al., 2010; Petry et al., 2013; Remschmidt et al., 2013). Worldwide, only a few population-based studies have focused on type-specific seroprevalence in men and women (Liu et al., 2016; Markowitz et al., 2009; Newall et al., 2008; Scherpenisse et al., 2012). The aim of our study was to determine the seroprevalence and associated risk factors of 19 HPV types in 18–79 year-old women and men living in Germany during the prevaccine era, using blood samples from a large countrywide population-based survey.

Subjects, materials, and methods

Study population and design

HPV seroprevalence was assessed by using archived serum samples from a cross-sectional population-based health survey. The German National Health Interview and Examination Survey 1998 (GNHIES98) was carried out by the Robert Koch Institute from October 1997 to March 1999. It was the first nationwide representative survey on the health status of Germany's adult population after the German reunification (Bellach et al., 1998). Participants were recruited using a two-stage stratified cluster sampling design (for a detailed description of the study design, see (Bellach et al., 1998; Scheidt-Nave et al., 2012)). In brief, the first stage selection comprised 120 cities and municipalities, representative regarding size, location and structure (urbanization, regional population density, and administrative borders) for all German communities. In the second stage a representative sample of the residential population aged 18–79 years was drawn from local population registers of the selected communities. In total 7,124 participants (response rate 61.4%) were interviewed, medically examined, and blood and urine samples were collected. Serum samples were stored at −20 °C. The study was conducted according to the Federal and State Commissioners for Data Protection guidelines and was approved by the Federal Commissioner for Data Protection. Informed consent was obtained from all participants.

Multiplex serology

In 2016/2017, the stored serum samples were tested for antibodies to the major capsid (L1) protein of 19 different HPV genotypes at the German Cancer Research Center (DKFZ) in Heidelberg. HPV types were selected for analysis based on the following criteria: public health relevance, carcinogenic potential, disease outcome, and genus- and species-specific broad distribution (for cutaneous types) (Supplementary Figure 1). The test panel included twelve mucosal (alpha: 6, 11, 16, 18, 31, 33, 35, 39, 45, 52, 58, 59) and seven cutaneous (alpha: 10; beta: 8, 38, 49; gamma: 4; nu: 41; mu: 1) HPV genotypes. Serological testing was done by a glutathione S-transferase (GST) capture immunoassay in combination with fluorescent bead technology as previously described (Waterboer et al., 2005). Type-specific HPV seroreactivity was measured in median fluorescence intensity (MFI) units and seropositivity was calculated based on previously established cut-off- values (Clifford et al., 2007). In addition, antibodies against the following other sexually transmitted infections (STI) were determined using the same assay: Mycoplasma genitalium (Mg), Herpes simplex virus 2 (HSV2) and Chlamydia trachomatis (Ct).

Statistical analysis

Seroprevalence was calculated for all 19 types separately and for the following groups of HPV types: HR types (HPV-HR: 16, 18, 31, 33, 35, 39, 45, 52, 58, 59), LR types: (HPV-LR: 6, 11), mucosal types (HPV-muc: 6, 11, 16, 18, 31, 33, 35, 39, 45, 52, 58, 59), cutaneous types (HPV-cut: 1, 4, 8, 10, 38, 41, 49), types included in the bivalent vaccine (HPV-2val: 16, 18), types included in the quadrivalent vaccine (HPV-4val: 6, 11, 16, 18), and types included in the nonavalent vaccine (HPV-9val: 6, 11, 16, 18, 31, 33, 45, 52, 58) (Supplementary Figure 1). Seroprevalence was calculated as the weighted proportion of participants seropositive to at least one of the HPV types included in one group. Differences regarding demographic and behavioral characteristic of participants stratified by sex were evaluated. All estimates were calculated by applying a survey weight, adopting the study sample to the population structure of Germany in 1997 in terms of age, sex, state, size of municipality, education, German/non-German nationality, and the regional distribution between East and West Germany (Thefeld et al., 1999). Age was categorized into 10-year groups (30–39, 40–49, 50–59, 60–69, 70–79), except for younger participants, which were categorized into the age groups 18–24 and 25–29 to be able to identify differences due to sexual behavior. Region of residence was split into two variables. Region of residence I, West and East Germany, takes into account the former boarders of the German Democratic Republic and the Federal Republic of Germany from 1949 to 1990. Region of Residence II describes the different states in Germany and is categorized into northern (Berlin, Brandenburg, Bremen, Hamburg, Lower Saxony, Mecklenburg-West Pomerania, Schleswig-Holstein), central (Hesse, North Rhine-Westphalia, Saxony, Saxony-Anhalt, Thuringia) and southern Germany (Baden-Württemberg, Bavaria, Rhineland-Palatinate, Saarland). Urbanity was categorized as rural (<5000 residents), small city (5000–<20,000 residents), medium-sized city (20,000–<100,000 residents) and large city (≥100,000 residents). Education refers to the highest academic qualification achieved and is categorized into low, middle and high based on the International Standard Classification of Education (ISCED) (1997). Seropositivity for any other sexually transmitted infection (STI+) was categorized as the status of being seropositive for at least one of the three tested STI. We categorized the lifetime number of sexual partners (LNSP) into the following groups: 0, 1, 2–4, 5–9, and ≥10 partners.

Chi2-Tests were used to test for statistical significance in categorical variables ($p < 0.05$) and logit transformation was

applied to calculate 95% confidence intervals (CI). Univariable analysis was applied to identify associations of various demographic and behavioral characteristics with type-specific and HPV group seropositivity. Multivariable weighted binomial regression models were developed estimating adjusted prevalence ratios and their 95% CI for females and males separately. All factors with a p-value <0.05 in univariable analysis were included in the multivariable regression model. Data management and statistical analysis were conducted using Stata, Version 14 (STATA Corp., College Station, TX, US).

Results

Serum samples of 6517 participants were successfully tested for HPV antibodies and included in this study (Figure 1). Included participants were not different to the full GNHIES98 sample regarding all baseline socio-demographic characteristics (Supplementary Table 1). Demographic characteristics of the participants are shown in Table 1.

Mucosal HPV types

Sex- and age-specific seroprevalences of the twelve mucosal HPV types are presented in Table 2. Seroprevalence ranged from 1.3% (HPV-33) to 12.0% (HPV-6). Overall seroprevalence of HPV types 6, 11, 16 and 18 were 12.8%, 4.8%, 8.7% and 6.9% among females, and 11.2%, 3.3%, 4.7% and 5.5% among males, respectively (Table 2). Analyzing all age groups together, we found slightly higher HPV seroprevalences of individual mucosal HPV types in females compared to males in all types except HPV-35.

Seroprevalences of the various HPV types differed by age group, showing heterogeneous age patterns. Among females, the lowest seroprevalences of mucosal HPV types were observed in the youngest age groups, except for HPV-6 and HPV-35, where lowest seroprevalences were found in the oldest age groups (Table 2). Compared to younger age groups, seroprevalences slightly increased in the 30–39 or 40–49-year-olds and remained relatively stable thereafter. Among females, HPV-16 seroprevalence increased from 5.0% in 18–24-year-olds to a first peak in 30–39-year-olds (9.6%) and had a second peak in the age group 60–69 years (10.7%; Table 2). The same pattern was also observed in HPV-6, HPV-11 and HPV-18 but with the first peak in 40–49-year-olds. Among males, the highest seroprevalence was found in the age group 30–59 years. For some HPV types (6, 11, 31, 45, and 52) we found a decrease in seroprevalence between 18–24-year-old and 25–29-year-old males. HPV-16 slightly increased from 2.7% in 18–24-year-olds to 4.5% in 25–29-year-olds and thereafter remained relatively stable with the highest prevalence of 5.7% among men aged 50–59 years.

There were only slight regional differences in type-specific HPV seroprevalence. HPV-16 seroprevalence was lowest among males in South Germany (3.4%, 95% CI 2.4%–4.7%) compared to North (5.2%, 95% CI 4.1%–6.6%) and central Germany (5.3%, 95% CI 4.2%–6.8%) (p = 0.042). Compared to males living in East Germany (5.9%, 95% CI 4.8%–7.4%), males in West Germany had lower HPV-16 seroprevalence (4.3%, 95% CI 3.6%–5.3%, p = 0.039). We observed no regional differences in HPV-16 seroprevalence among females (data not shown).

Cutaneous HPV types

Type-specific cutaneous HPV seroprevalence ranged from 8.7% (HPV-41) to 34.7% (HPV-4). The most prevalent cutaneous HPV types were 1, 4, and 8 with 34.5%, 33.9%, 18.3% among females, and

Table 1
Demographic Characteristics of the Study Participants by Sex, HPV Seroprevalence Study (n = 6517), 2016/2017 (sera collected 1997–1999).

	Females		Males	
	Subjects, No.	%[a]	Subjects, No.	%[a]
Overall	3,356	50.6	3,161	49.4
Age group (y)				
18–24	305	9.4	342	10.0
25–29	274	9.2	237	9.2
30–39	729	21.4	709	24.2
40–49	635	17.8	588	19.1
50–59	636	16.5	624	17.1
60–69	492	14.7	448	13.5
70–79	285	11.0	213	6.8
Region of Residence I				
East	1,165	20.9	1,060	20.9
West	2,191	79.1	2,101	79.1
Region of Residence II				
Northern Germany	872	25.8	794	26.4
Central Germany	1,535	41.1	1,454	40.7
Southern Germany	949	33.1	913	33.0
Country of Birth				
Germany	2,943	83.8	2,797	84.1
Other	315	13.5	286	13.2
NA	98	2.7	78	2.7
Urbanity				
Rural	787	20.1	758	20.3
Small City	694	18.8	694	20.6
Medium-sized City	863	28.5	784	27.0
Large City	1,012	32.6	925	32.1
History of Smoking				
No	1,823	54.6	1,070	33.4
Yes	1,443	42.8	2,029	64.4
NA	90	2.6	62	2.3
Education				
Low	736	29.6	378	16.7
Middle	1,960	53.4	1,695	54.0
High	562	14.2	1,011	26.5
NA	98	2.7	77	2.8
Seropositive for any other STI				
No	1,462	44.2	1,344	42.3
Yes	1,894	55.8	1,817	57.7
Lifetime sex partners				
0	29	1.1	30	0.9
1	702	20.9	442	13.6
2–4	838	24.0	604	18.4
5–9	311	9.3	402	12.4
≥10	136	3.9	387	12.8
NA	1,340	40.9	1,296	41.8
History of Use of Contraceptives				
No	2,637	79.8	–	–
Yes	704	19.8	–	–
NA	15	0.5	–	–

NA, not available.
[a] Weighted percentage STI, sexually transmitted infection (i.e. Mycoplasma genitalium, Herpes simplex virus 2, or Chlamydia trachomatis).

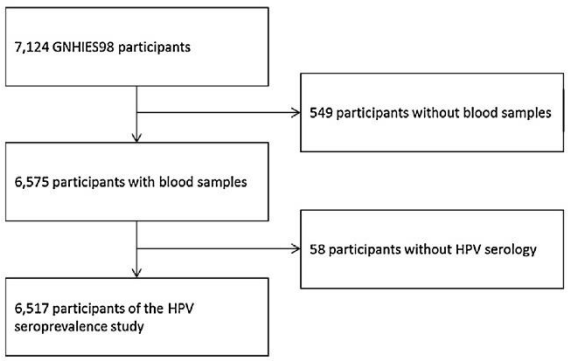

Figure 1. Flow chart of study participants of the HPV seroprevalence study, 2016/2017. Sera were collected throughout the German National Health Interview and Examination Survey (GNHIES98).1997–1999.

Table 2
Seroprevalence of Individual Mucosal Human Papillomavirus Types by Sex and Age, HPV Seroprevalence Study (n = 6517), 2016/2017 (sera collected 1997–1999).

Group	Subjects, no.	Seroprevalence by HPV type, % (95% CI)												
		6[#]	11[#]	16[#]	18	31	33	45	52	58	35	39	59
Overall	**6517**	**12.0 (11.1–13.0) 782**	**4.1 (3.4–4.8) 253**	**6.7 (6.0–7.4) 455**	**6.2 (5.5–7.0) 395**	**3.2 (2.7–3.7) 204**	**1.2 (0.9–1.6) 82**	**2.6 (2.2–3.1) 165**	**2.0 (1.6–2.5) 121**	**4.0 (3.4–4.7) 262**	**5.8 (5.1–6.6) 376**	**8.3 (7.5–9.1) 543**	**9.6 (8.8–10.5) 629**
Female, overall	**3356**	**12.8 (11.7–14.1) 439**	**4.8 (4.0–5.8) 161**	**8.7 (7.6–9.8) 299**	**6.9 (5.9–7.9) 228**	**3.5 (2.9–4.3) 119**	**1.3 (0.9–1.8) 47**	**3.0 (2.4–3.7) 101**	**2.2 (1.7–3.0) 67**	**4.2 (3.5–5.1) 143**	**5.3 (4.4–6.3) 176**	**8.7 (7.7–9.9) 306**	**10.2 (9.1–11.5) 355**
Age groups													
18–24	305	8.5 (5.4–13.3) 28	2.2 (1.1–4.7) 8	5.0 (3.0–8.2) 15	4.8 (2.7–8.4) 13	3.3 (1.8–6.1) 10	0.5 (0.1–2.2) 2	1.0 (0.3–2.9) 4	0.7 (0.1–3.2) 2	0.9 (0.2–3.3) 3	4.0 (2.0–7.9) 13	6.1 (3.5–10.5) 17	6.5 (4.0–10.3) 19
25–29	274	14.3 (10.0–20.0) 37	4.5 (2.1–9.7) 11	7.4 (4.4–12.4) 19	6.2 (3.7–10.2) 17	2.3 (1.1–4.8) 7	0.2 (0.0–1.7) 1	1.0 (0.4–2.8) 4	0.8 (0.2–3.3) 2	3.6 (1.7–7.4) 10	5.3 (3.0–9.0) 15	5.5 (2.9–10.3) 11	8.0 (5.2–12.0) 22
30–39	729	14.6 (11.9–17.9) 111	5.0 (3.5–7.0) 37	9.6 (7.5–12.2) 75	6.9 (5.0–9.5) 51	4.7 (3.2–6.9) 32	0.6 (0.2–1.4) 5	3.2 (2.2–4.8) 25	1.7 (0.9–3.2) 10	6.8 (4.9–9.2) 47	6.9 (5.0–9.5) 46	7.7 (5.7–10.2) 66	9.8 (7.7–12.5) 82
40–49	635	16.1 (13.3–19.3) 102	5.5 (3.8–7.9) 34	8.2 (6.2–10.7) 55	8.1 (6.0–10.7) 51	3.6 (2.2–5.7) 22	1.8 (0.9–3.4) 12	3.6 (2.2–5.8) 22	2.0 (1.1–3.4) 13	5.6 (4.1–7.6) 40	5.2 (3.6–7.4) 36	10.5 (8.1–13.5) 68	10.8 (8.1–14.2) 70
50–59	636	10.5 (8.0–13.7) 67	4.2 (2.8–6.5) 28	9.3 (7.1–12.0) 57	5.9 (4.0–8.5) 36	2.9 (1.7–4.9) 20	2.4 (1.3–4.6) 13	2.0 (1.0–4.1) 12	2.5 (1.3–5.0) 12	2.7 (1.5–4.9) 15	5.0 (3.2–7.8) 28	10.4 (8.0–13.4) 64	10.0 (7.7–13.1) 66
60–69	492	14.5 (11.2–18.7) 67	5.7 (3.6–8.7) 27	10.7 (7.4–15.2) 54	8.2 (5.8–11.5) 40	3.6 (2.2–5.8) 19	1.6 (0.8–3.3) 9	4.4 (2.6–7.2) 20	3.6 (2.0–6.4) 15	4.3 (2.5–7.5) 19	3.8 (2.4–6.1) 20	10.8 (8.1–14.3) 57	14.2 (11.1–17.9) 66
70–79	285	7.6 (5.1–11.3) 27	5.6 (2.9–10.6) 16	8.1 (5.1–12.7) 24	6.9 (4.3–11.0) 20	3.3 (1.3–8.0) 9	1.5 (0.6–4.0) 5	4.5 (2.6–7.8) 14	4.1 (2.0–8.4) 13	2.3 (0.8–6.6) 9	5.6 (3.1–10.0) 18	7.7 (4.5–12.6) 23	10.4 (7.0–15.1) 30
Males, overall	**3161**	**11.2 (10.0–12.5) 343**	**3.3 (2.5–4.2) 92**	**4.7 (4.0–5.5) 156**	**5.5 (4.5–6.7) 167**	**2.8 (2.2–3.6) 85**	**1.1 (0.7–1.7) 35**	**2.2 (1.7–2.9) 64**	**1.7 (1.2–2.3) 54**	**3.8 (3.1–4.7) 119**	**6.4 (5.4–7.4) 200**	**7.8 (6.8–9.0) 237**	**9.0 (7.9–10.3) 274**
Age groups													
18–24	342	12.5 (8.8–17.4) 42	3.5 (1.8–6.7) 11	2.7 (1.4–5.2) 9	4.9 (3.0–7.9) 18	2.6 (1.4–4.9) 9	0.5 (0.1–2.1) 2	2.2 (1.1–4.4) 8	1.7 (0.8–3.7) 7	3.3 (1.7–6.4) 11	5.6 (3.6–8.7) 19	5.2 (3.2–8.5) 20	6.1 (3.9–9.3) 25
25–29	237	9.0 (5.6–14.1) 22	0.8 (0.2–3.6) 2	4.5 (2.3–8.5) 13	5.5 (3.3–9.2) 14	1.5 (0.6–3.8) 5	0.5 (0.1–3.6) 1	1.7 (0.7–4.5) 5	1.0 (0.3–3.3) 3	3.3 (1.5–7.0) 8	7.7 (4.6–12.6) 18	6.1 (3.5–10.4) 14	10.9 (6.6–17.4) 26
30–39	709	14.3 (11.5–17.6) 96	5.0 (3.4–7.2) 30	4.7 (3.3–6.7) 35	5.5 (3.6–8.5) 33	3.7 (2.2–6.3) 20	1.9 (0.9–3.9) 11	2.9 (1.6–5.3) 17	2.3 (1.2–4.3) 12	6.2 (4.4–8.7) 43	7.2 (5.2–9.9) 50	7.9 (5.9–10.6) 53	7.2 (5.3–9.6) 48
40–49	588	15.5 (12.3–19.2) 83	3.8 (2.2–6.4) 18	5.4 (3.5–8.1) 30	5.0 (3.0–8.3) 24	3.1 (1.9–4.8) 18	1.5 (0.8–2.8) 10	1.8 (0.8–4.0) 8	2.1 (1.0–4.2) 10	5.7 (3.6–8.7) 34	7.2 (5.1–9.9) 40	7.2 (5.1–10.0) 38	7.4 (5.3–10.2) 42
50–59	624	7.4 (5.6–9.8) 49	2.3 (1.3–4.0) 12	5.7 (4.2–7.7) 37	6.4 (4.6–8.8) 39	2.6 (1.6–4.2) 18	0.8 (0.4–2.0) 6	1.8 (1.0–3.2) 12	1.5 (0.8–2.7) 11	2.6 (1.5–4.5) 15	5.2 (3.6–7.4) 33	9.3 (6.9–12.5) 52	11.1 (8.4–14.4) 63
60–69	448	7.4 (5.2–10.5) 40	2.8 (1.6–4.8) 14	4.0 (2.6–6.2) 22	5.4 (3.4–8.3) 25	2.1 (1.1–3.8) 10	0.5 (0.1–2.0) 2	2.8 (1.4–5.5) 10	1.1 (0.5–2.4) 7	0.5 (0.2–1.4) 4	4.6 (2.9–7.2) 25	9.0 (6.6–12.1) 40	11.6 (8.7–15.2) 48
70–79	213	5.7 (3.1–10.3) 11	2.2 (0.9–5.6) 5	4.3 (2.2–8.2) 10	5.7 (3.1–10.3) 14	2.6 (1.1–6.5) 5	1.1 (0.3–3.6) 3	1.3 (0.5–3.6) 4	1.1 (0.4–3.2) 4	1.3 (0.5–3.7) 4	6.7 (3.8–11.4) 15	9.0 (5.6–14.2) 20	11.3 (7.6–16.4) 22

Note. CI, confidence interval.
[#] Female overall vs male overall, $p < 0.05$.

33.6%, 35.6%, 19.6% among males, respectively. Additional data on cutaneous HPV seroprevalence are provided in Supplementary Table 2. Compared to mucosal types, we did not find any significant type-specific differences between both sexes. For some cutaneous HPV types, i.e., 8, 10, 38 and 49, we observed a general increase in HPV seroprevalence with age. The age pattern of HPV-1 clearly differed with a steady decrease from 46.4% to 21.3% among females and 39.8% to 26.6% among males.

Grouped HPV types

Seropositivity against at least one mucosal HPV type (HPV-muc, 35.3%) or any HPV-HR type (HPV-HR, 27.9%) showed slight but statistically significant higher seroprevalences in females as compared to male participants (Table 3). This constellation was also observed in other subgroups (HPV-2val, HPV-4val, HPV-9val, HPV-LR), reflecting mainly the sex-specific seroprevalence differences in HPV-6, HPV-11 and HPV-16. Age-specific seroprevalences for HPV types included in the vaccines and for those assigned to the HR and LR group are shown in Figure 2 and Figure 3.

Multiple seropositivity

While 18.4% were positive for only one HPV-HR type, 4.9% were positive for two and 4.6% for ≥3 different HPV-HR types (Supplementary Table 3). There was no significant difference in this distribution between females and males.

Risk factors

The risk factor analysis was restricted to HPV types included in the 4-valent vaccine and the HR and LR type groups. The results related to HPV-16 are shown in Table 4; the remaining results are shown in the supplement (Supplementary Table 4–Supplementary Table 8). In univariable analysis, STI+, LNSP, age and urbanity were significantly associated with HPV-16 seropositivity among females (Table 4), and were therefore included in our final multivariable model. In the model, all variables remained significantly associated with HPV-16 seropositivity except age. Females living in medium-sized cities were more likely to be seropositive than females living in rural areas, small or large cities. STI+ females as well as females with higher LNSP were more likely to be HPV-16 seropositive. Among males, STI+, LNSP, age and region of residence were significantly associated with HPV-16 seropositivity in the univariable analysis. In the multivariable analysis, STI+ was associated with higher HPV-16 seropositivity, while living in the southern part of Germany was associated with lower HPV-16 seropositivity.

Discussion

We assessed the prevalence of antibodies against 19 different mucosal and cutaneous HPV types in the adult population in Germany before the introduction of routine female HPV vaccination. Therefore, these data provide an estimate of naturally acquired and cumulative type-specific HPV exposure (Robbins et al., 2014). Being positive for any HPV type included in the recently licensed 9-valent HPV vaccine was common with 26.9% among females and 22.8% among males. Being seropositive for any other tested STI and having a higher lifetime number of sexual partners were the strongest factors associated with HPV-16 seropositivity.

Most previous studies on HPV infections in Germany were based on HPV DNA in genital samples collected from young women (Delere et al., 2014; Iftner et al., 2010; Petry et al., 2013). Using this approach, one study showed that HPV-16 was the predominant vaccine-relevant HPV-HR genotype in Germany with 19.5% among 20–22-year-old females (Delere et al., 2014). This was also observed in other HPV DNA studies in Germany and is in accordance with data collected worldwide (Bruni et al., 2010; de Sanjose et al., 2007; Iftner et al., 2010; Petry et al., 2013). Compared

Table 3
Seroprevalence of grouped Human Papillomavirus (HPV) Types by Sex, HPV Seroprevalence Study (n = 6517), 2016/2017 (sera collected 1997–1999).

		Seroprevalence, % (95% CI)		
HPV types, grouped	Overall	Female	Male	p-Value*
≥1 of 2-valent vaccine (HPV-2val)	10.7 (9.9–11.6)	12.7 (11.4–14.1)	8.7 (7.5–9.9)	<0.01
≥1 of 4-valent vaccine (HPV-4val)	20.6 (19.5–21.8)	22.9 (21.3–24.6)	18.3 (16.9–19.8)	<0.01
≥1 of 9-valent vaccine (HPV-9val)	24.9 (23.7–26.1)	26.9 (25.1–28.8)	22.8 (21.4–24.3)	<0.01
≥1 of mucosal (HPV-muc)	35.3 (33.7–36.8)	36.9 (34.8–39.0)	33.6 (31.7–35.6)	<0.05
≥1 of cutaneous (HPV-cut)	63.6 (61.9–65.2)	62.5 (60.6–64.4)	64.7 (62.2–67.0)	0.14
≥1 of High Risk (HPV-HR)	27.9 (26.4–29.4)	29.3 (27.3–31.4)	26.4 (24.5–28.3)	<0.05
≥1 of Low Risk (HPV-LR)	13.3 (12.3–14.4)	14.6 (13.2–16.0)	12.0 (10.8–13.4)	<0.01

* Females vs males.

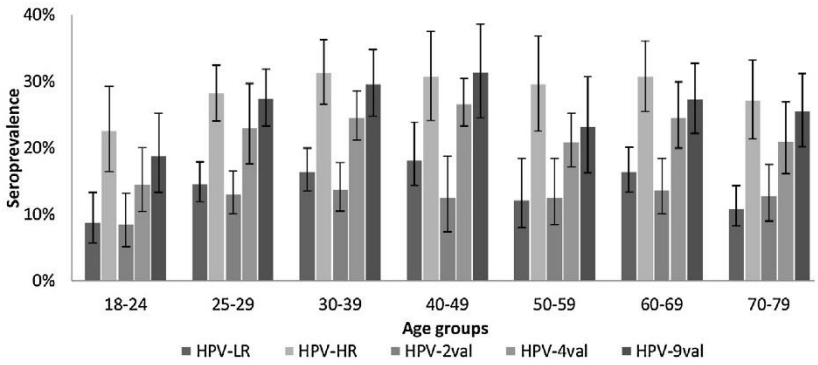

Figure 2. Seropositivity of grouped Human Papillomavirus (HPV) types in 3356 females living in Germany by age (HPV-LR: ≥1 of 6 or 11; HPV-HR: ≥1 of 16 or 18; HPV-2val: ≥1 of 6 or 11; HPV-4val: ≥1 of 6, 11, 16 or 18; HPV-9val: ≥1 of 6, 11, 16, 18, 31, 33, 45, 52 or 58). HPV seroprevalence study 2016/2017 (sera collected 1997–1999).

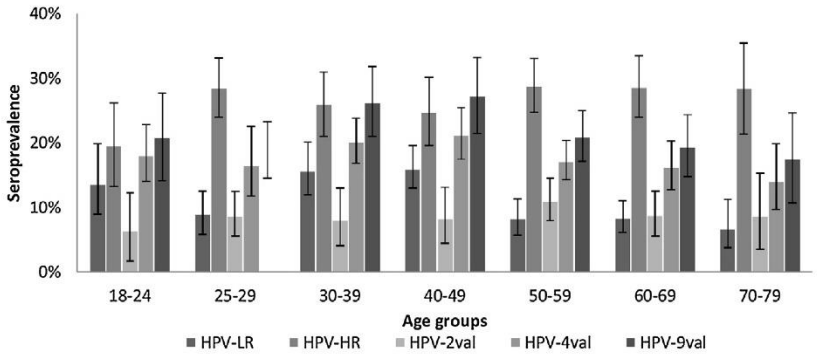

Figure 3. Seropositivity of grouped Human Papillomavirus (HPV) types in 3161 males by age (HPV-LR: ≥1 of 6 or 11; HPV-HR: ≥1 of 16 or 18; HPV-2val: ≥1 of 6 or 11; HPV-4val: ≥1 of 6, 11, 16 or 18; HPV-9val: ≥1 of 6, 11, 16, 18, 31, 33, 45, 52 or 58). HPV seroprevalence study 2016/2017 (sera collected 1997–1999).

Table 4
Factors Associated with Seropositivity to Human Papillomavirus Type 16 Stratified by Sex, HPV Seroprevalence Study, 2016/2017 (sera collected 1997–1999).

Variable		Females		Males	
		Crude PR (95% CI)	Fully aPR (95% CI) [$]	Crude PR (95% CI)	Fully aPR (95% CI) [$]
Age groups (y)					
	18–24	Reference	Reference	Reference	Reference
	25–29	1.49 (0.69–3.18)	1.17 (0.54–2.53)	1.68 (0.64–4.40)	1.61 (0.61–4.22)
	30–39	**1.91 (1.09–3.35)**	1.45 (0.83–2.55)	1.76 (0.81–3.84)	1.51 (0.67–3.42)
	40–49	1.63 (0.93–2.87)	1.21 (0.69–2.10)	2.00 (0.86–4.62)	1.67 (0.71–3.93)
	50–59	**1.85 (1.06–3.23)**	1.45 (0.84–2.50)	**2.12 (1.03–4.38)**	1.90 (0.90–4.00)
	60–69	**2.13 (1.16–3.93)**	1.61 (0.90–2.89)	1.51 (0.69–3.29)	1.32 (0.59–2.94)
	70–79	1.62 (0.85–3.08)	1.16 (0.61–2.20)	1.61 (0.61–4.27)	1.43 (0.53–3.88)
Region of residence I					
	East Germany	Reference	na*	Reference	Reference
	West Germany	0.81 (0.65–1.02)	na*	**0.73 (0.55–0.98)**	0.89 (0.65–1.22)
Region of residence II					
	Northern Germany	Reference	na*	Reference	Reference
	Central Germany	1.17 (0.86–1.60)	na*	1.02 (0.73–1.43)	1.04 (0.75–1.44)
	Southern Germany	1.03 (0.71–1.48)	na*	**0.64 (0.43–0.97)**	0.69 (0.45–1.07)
Country of birth					
	Germany	Reference	na*	Reference	na*
	Other	1.01 (0.63–1.62)	na*	0.88 (0.43–1.80)	na*
Urbanity					
	Rural	Reference	Reference	Reference	na*
	Small city	0.94 (0.63–1.40)	0.95 (0.64–1.39)	1.25 (0.75–2.06)	na*
	Medium-sized city	**1.44 (1.02–2.02)**	**1.48 (1.07–2.04)**	1.47 (0.94–2.30)	na*
	Large city	1.06 (0.74–1.51)	1.01 (0.72–1.43)	1.26 (0.83–1.91)	na*
History of smoking					
	No	Reference	na*	Reference	na*
	Yes	1.12 (0.86–1.46)	na*	0.73 (0.51–1.06)	na*
Education					
	Low	1.24 (0.90–1.72)	na*	0.81 (0.41–1.59)	na*
	Middle	Reference	na*	Reference	na*
	High	0.95 (0.68–1.32)	na*	1.12 (0.81–1.55)	na*
Seropositive for any other STI					
	No	Reference	Reference	Reference	Reference
	Yes	**2.48 (1.84–3.34)**	**2.29 (1.67–3.12)**	**2.73 (1.72–4.35)**	**2.51 (1.56–4.04)**
Lifetime no. of sex partners					
	0	no+	no+	2.65 (0.53–13.16)	3.08 (0.63–15.09)
	1	Reference	Reference	Reference	Reference
	2–4	1.31 (0.91–1.88)	1.23 (0.85–1.79)	1.46 (0.66–3.20)	1.36 (0.63–2.93)
	5–9	**2.17 (1.33–3.52)**	**1.83 (1.10–3.04)**	1.70 (0.76–3.81)	1.55 (0.70–3.41)
	> = 10	**2.40 (1.39–4.13)**	**1.97 (1.07–3.63)**	**2.46 (1.24–4.87)**	**2.00 (1.02–3.93)**
	NA	**1.85 (1.25–2.74)**	**1.63 (1.13–2.36)**	**2.09 (1.18–3.71)**	**1.88 (1.07–3.29)**
History of use of oral contraceptives					
	No	Reference	na*	–	–
	Yes	1.02 (0.77–1.35)	na*	–	–

Abbreviations: aPR, adjusted prevalence ratio; CI, confidence interval; na, not available; STI, sexually transmitted infection.
na* variables were not significantly associated with HPV seroprevalence in the univariable model and therefore not included in the fully adjusted model.
no+ no observations in categories.
$ the aPR are adjusted for all variables which are listed in the table and remained in the final model.
Statistically significant PR are shown in **bold font**.

to other vaccine-relevant HPV-HR types, HPV-16 was also the most prevalent in our study, which is in agreement with previous HPV seroprevalence studies (Liu et al., 2016; Scherpenisse et al., 2012), even though comparing serological results based on different assays remains difficult. Apart from methodological differences, heterogeneity in HPV-16 seroprevalence among populations in different countries and regions has to be taken into account (Vaccarella et al., 2010). In general, HPV-16 seroprevalence was lower in our study compared to other population-based seroprevalence studies (Liu et al., 2016; Markowitz et al., 2009; Newall et al., 2008; Wang et al., 2003). However, in a seroprevalence study with sera from 34–82-year-old adults in Germany collected in the late 1980s, HPV-16 seroprevalence among females was only slightly higher than in our study (10.4%), and nearly the same for males (4.3%) (Michael et al., 2008). Regarding the four vaccine-relevant HPV types 6, 11, 16 and 18, we observed similar results with the highest seroprevalence in HPV-6 as reported in other population-based HPV seroprevalence studies (Introcaso et al., 2014; Liu et al., 2016; Markowitz et al., 2009; Newall et al., 2008).

The overall lower seroprevalence in mucosal HPV types among males compared to females is consistent with other studies (Markowitz et al., 2009; Michael et al., 2008; Newall et al., 2008; Scherpenisse et al., 2012), even though the quantitative difference of HPV seroprevalence between men and women varies. While population studies in the US (Markowitz et al., 2009) and England (Desai et al., 2011) showed a greater difference (depending on the HPV types) in seroprevalence between women and men, the observed differences were less strong in our results as also observed in other population surveys in the Netherlands (Scherpenisse et al., 2012) or Australia (Newall et al., 2008). The overall sex difference has not been observed in studies using HPV DNA assays, where men had similar HPV infection rates and a relative stable risk for acquiring new HPV infections over age (Dunne et al., 2006; Giuliano et al., 2011). The difference in mucosal HPV seroprevalence might be a result of a different (keratinized) epithelium at the infection site, but has also been attributed to a shorter average duration of infection in men, leading to a reduced chance of developing HPV antibodies (Carter et al., 2000; Markowitz et al., 2009). Our present findings showed that HPV-4val seropositivity peaked later among men (40–49-year-olds) than among women, which was comparable to seroprevalence data from Australia (32% at 40–49-year-olds) and the US (18% at 50–59-year-olds) (Markowitz et al., 2009; Newall et al., 2008).

Population-wide surveys offer the opportunity to draw conclusions on trends over age groups. We observed a slight increase in HPV-HR seroprevalence mainly among females in the youngest age groups, from 18 to 24 years to 30–39 years, which is consistent with other seroprevalence studies (Liu et al., 2016), probably reflecting the onset of sexual activity and the increasing number of sex partners in those age groups. HPV-4val among females was generally lower and reached a later age peak with 26.7% in 40–49-year-olds compared to peak seropositivity at 30–39-year-olds in Australia (39%) and the US (42%) (Markowitz et al., 2009; Newall et al., 2008). We also observed a lower HPV-9val seropositivity in females in our study as compared to a study from the US (40.5%), while HPV-9val prevalence in males was comparable between these two studies (Markowitz et al., 2009).

In contrast to other studies, we did not observe in older age groups a lower seroprevalence in vaccine-relevant HPV types, except for HPV6 and HPV58 in males. This lower seroprevalence in older age groups was explained by other authors as a result of cohort effects or waning antibodies, even though the humoral response is considered to be relatively stable over time (Newall et al., 2008; Ryser et al., 2017; Tiggelaar et al., 2012; Wang et al., 2003). In general, HPV prevalences in men are described to be less influenced by age compared to women (Giuliano et al., 2011). However, in our study a relatively stable age-related seroprevalence trend was observed in both sexes.

Previous studies described a second peak in HPV DNA prevalence among older women in some but not all geographic regions (Castle et al., 2005; de Sanjose et al., 2007; Gravitt et al., 2013; Trottier et al., 2010). However, this second peak was not observed in most population-based seroprevalence studies (Liu et al., 2016; Markowitz et al., 2009; Newall et al., 2008). Despite a relatively stable seroprevalence over age in our present findings, we observed a second age peak in HPV seroprevalence for some HPV types (6, 11, 16, 39, 58, and 59) among 60–69-year-old women. The second age peak in older women is discussed as a menopause-related hormonal change which possibly reactivates latent HPV infections (Althoff et al., 2009; Castle et al., 2005; de Sanjose et al., 2007; Gravitt et al., 2013; Gravitt and Winer, 2017). Another hypothesis is that the peak might reflect new HPV infections because of sexual behavior change in women of older ages and their partners (Trottier et al., 2010). However, it is also discussed that seroprevalence differences in older women are a cohort effect (de Sanjose et al., 2007; Ryser et al., 2017; Trottier and Franco, 2006).

As compared to individual mucosal HPV seroprevalence among older age groups, our data showed that HPV seroprevalence in the youngest age groups was relatively high. The HPV-HR seroprevalence of nearly 10% in 18–24-year-old participants underlines the importance of vaccination at a young age before sexual debut. However, the observed second peak of individual mucosal HPV seroprevalence indicates that in older women reactivation of prior infections as well as incident HPV infections should be considered.

Type- and age-specific seroprevalence of cutaneous HPV types was comparable with other studies with an age-related increase in cutaneous HPV types except for HPV-1 (Antonsson, 2012; Rahman et al., 2016b). Since HPV-1- and HPV-4-related warts are common among children and adolescents the high prevalence of HPV-1 and HPV-4 among the youngest participants of our study is not an unexpected finding (Antonsson, 2012).

Behavioral factors associated with seropositivity in our study were similar to those reported elsewhere (Liu et al., 2016; Markowitz et al., 2009). Age was associated with HPV-16 seropositivity in both sexes only in univariable analysis. In the final model, independent predictors of HPV-16 seropositivity were the presence of antibodies to other STI and LNSP, which was similar to those reported elsewhere (Liu et al., 2016; Scherpenisse et al., 2012; Vaccarella et al., 2010; Wang et al., 2003). Given that being STI+ was the strongest associated factor in nearly all HPV types, STI + could be a useful marker of sexual behavior, in addition to the potentially biased self-reported LNSP. In contrast to previous studies (Liu et al., 2016; Rahman et al., 2016a; Vaccarella et al., 2010), we did not observe any association between age and HPV-16 and HPV-18 seropositivity, which could be explained by different age categorizations.

Several studies have supported HPV antibody seropositivity as a biomarker of past HPV exposure (Hariri et al., 2008; Liu et al., 2016; Markowitz et al., 2009; Newall et al., 2008; Wang et al., 2003). In our study, seropositivity was measured by a GST fusion protein-based multiplex serological assay that has been used in several other HPV seroprevalence studies (Clifford et al., 2007; Michael et al., 2008; Rahman et al., 2016a; Rahman et al., 2016b; Wilson et al., 2014). However, our prevalence data may not be directly comparable with studies using different antigen preparations (e.g. virus-like particles) and other cut-off definitions in their assays. Besides these technique-based differences, seroprevalence differences between countries may also be explained by underlying populations, sampling time, and differences in exposures related to HPV transmission like sexual behaviors. Seropositivity is not a perfect HPV exposure measure as it tends to underestimate the

cumulative exposure (Introcaso et al., 2014). This is due to various factors, i.e., the impact of a broad range of sex-, type- and infection site-specific seroconversion rates, infection clearance and the still unknown seropositivity duration (Brouwer et al., 2015; Carter et al., 2000; Edelstein et al., 2011; Giuliano et al., 2015; Lu et al., 2012). Furthermore, natural HPV infections result in much lower immune response and seroconversion rates, compared to HPV vaccination (Harper et al., 2006). Therefore, the presented estimates of seroprevalence also might be an underestimation of cumulative HPV exposure.

Our study has several strengths. It was based on a large, representative sample of the population of Germany, and a large demographic and behavioral data set; blood samples were collected using highly standardized sampling methods. Using these blood samples from the prevaccine era, we were able to measure naturally acquired antibodies to 19 mucosal and cutaneous HPV types in a single laboratory test. In addition, the antibody prevalence against other common STI was used as a proxy for sexual activity. Finally, using nationally representative data of GNIEHS98 it was possible to estimate the type-specific HPV seroprevalence in demographic groups in Germany and to identify factors associated with type-specific seropositivity in men and women.

However, we are also aware of some limitations of our study which should be considered when interpreting the results. Serum samples were properly stored at −20 °C since the collection in 1997–1999, but storage time could still have an effect on sera quality and antibody concentration. However, this would affect all samples and could not explain group-specific differences, like age-, sex- or type-specific prevalence.

In conclusion, we generated data on type-specific HPV seroprevalence in the general population of adults living in Germany, for all age groups and both sexes. These data were collected before HPV vaccine introduction and will serve as baseline estimates for naturally derived cumulative type-specific HPV exposure in Germany in non-vaccinated individuals. HPV seroprevalence studies in the adult population after vaccine introduction as well as in children and adolescents are currently underway in Germany and can be used to assess the population-level (indirect) effects of HPV vaccination, which has been initially carried out in Germany mainly with 4-valent and since 2016 mainly with 9-valent HPV vaccines.

Conflict of interest

A.L., C.P.-M., M.P., M.T., T.H., T.W., J.S., Y.D., O.W., M.W.-P. declared that they have no conflict of interest.

Funding statement

This work was supported by the German Federal Ministry of Health (BMG) and by in-house funding of the Molecular Diagnostics of Oncogenic Infections Division at the German Cancer Research Center (DKFZ) in Heidelberg/Germany. The funding source had no involvement in the study design and the preparation, review or approval of the manuscript.

Ethical approval

Although there was no law or regulation on Ethic Committees in Germany at the time of the conduct of the study, the study was approved by the Board of the Federal Commissioner for Data Protection Berlin, Germany. The study was conducted according to the Federal and State Commissioners for Data Protection guidelines. Informed written consent and assent were obtained from all participants.

Meetings information

Part of the data was presented at the EUROGIN 2016 Congress, Salzburg/Austria, June 15–18, 2016 and the 31st International Papillomavirus Conference (HPV 2017), Cape Town/South Africa, 28 February–5 March 2017.

Author contribution

Analyzed the data: AL; Developed the IgG Multiplex assay and did the experiments for the study: TW, MP; Collected data for the study: CPM, MT, TW; Wrote the first draft of the paper: AL; Contributed to the writing of the paper: AL, MWP, TH, CPM, MT, TW, MP, OW, JS; Conception and design of the study: YD, MP, MWP, OW.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.03.022.

References

Abreu AL, Souza RP, Gimenes F, Consolaro ME. A review of methods for detect human Papillomavirus infection. Virol J 2012;9:262.
Althoff KN, Paul P, Burke AE, Viscidi R, Sangaramoorthy M, Gravitt PE. Correlates of cervicovaginal human papillomavirus detection in perimenopausal women. J Women Health 2009;18(9):1341–6.
Antonsson A. Review: antibodies to cutaneous human papillomaviruses. J Med Virol 2012;84(5):814–22.
Antonsson A, Forslund O, Ekberg H, Sterner G, Hansson BG. The ubiquity and impressive genomic diversity of human skin papillomaviruses suggest a commensalic nature of these viruses. J Virol 2000;74(24):11636–41.
Bellach BM, Knopf H, Thefeld W. The German Health Survey. 1997/98. Gesundheitswesen (Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany)) 1998;60(Suppl 2):S59–68.
Brouwer AF, Eisenberg MC, Carey TE, Meza R. Trends in HPV cervical and seroprevalence and associations between oral and genital infection and serum antibodies in NHANES 2003-2012. BMC Infect Dis 2015;15:575.
Bruni L, Diaz M, Castellsague X, Ferrer E, Bosch FX, de Sanjose S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J Infect Dis 2010;202(12):1789–99.
Carter JJ, Koutsky LA, Hughes JP, Lee SK, Kuypers J, Kiviat N, et al. Comparison of human papillomavirus types 16, 18, and 6 capsid antibody responses following incident infection. J Infect Dis 2000;181(6):1911–9.
Castle PE, Schiffman M, Herrero R, Hildesheim A, Rodriguez AC, Bratti MC, et al. A prospective study of age trends in cervical human papillomavirus acquisition and persistence in Guanacaste, Costa Rica. J Infect Dis 2005;191(11):1808–16.
Clifford GM, Shin HR, Oh JK, Waterboer T, Ju YH, Vaccarella S, et al. Serologic response to oncogenic human papillomavirus types in male and female university students in Busan, South Korea. Cancer Epidemiol Biomarkers Prev 2007;16(9):1874–9.
de Sanjose S, Diaz M, Castellsague X, Clifford G, Bruni L, Munoz N, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet Infect Dis 2007;7(7):453–9.
de Villiers EM, Fauquet C, Broker TR. Bernard HU, zur Hausen H. Classification of papillomaviruses. Virology 2004;324(1):17–27.
Delere Y, Remschmidt C, Leuschner J, Schuster M, Fesenfeld M, Schneider A, et al. Human Papillomavirus prevalence and probable first effects of vaccination in 20 to 25 year-old women in Germany: a population-based cross-sectional study via home-based self-sampling. BMC Infect Dis 2014;14:87.
Desai S, Chapman R, Jit M, Nichols T, Borrow R, Wilding M, et al. Prevalence of human papillomavirus antibodies in males and females in England. Sex Transm Dis 2011;38(7):622–9.
Dunne EF, Nielson CM, Stone KM, Markowitz LE, Giuliano AR. Prevalence of HPV infection among men: a systematic review of the literature. J Infect Dis 2006;194(8):1044–57.
Edelstein ZR, Carter JJ, Garg R, Winer RL, Feng Q, Galloway DA, et al. Serum antibody response following genital {alpha}9 human papillomavirus infection in young men. J Infect Dis 2011;204(2):209–16.
Giuliano AR, Lee JH, Fulp W, Villa LL, Lazcano E, Papenfuss MR, et al. Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. Lancet 2011;377(9769):932–40.
Giuliano AR, Viscidi R, Torres BN, Ingles DJ, Sudenga SL, Villa LL, et al. Seroconversion following anal and genital HPV infection in men: the HIM study. Papillomavirus Res 2015;1:109–15.
Gravitt PE, Rositch AF, Silver MI, Marks MA, Chang K, Burke AE, et al. A cohort effect of the sexual revolution may be masking an increase in human papillomavirus detection at menopause in the United States. J Infect Dis 2013;207(2):272–80.

Gravitt PE, Winer RL. Natural history of HPV infection across the lifespan: role of viral latency. Viruses 2017;9(10).
Hariri S, Dunne EF, Sternberg M, Unger ER, Meadows KS, Karem KL, et al. Seroepidemiology of human papillomavirus type 11 in the United States: results from the third National Health And Nutrition Examination Survey, 1991–1994. Sex Transm Dis 2008;35(3):298–303.
Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet 2006;367(9518):1247–55.
Hauck F, Oliveira-Silva M, Dreyer JH, Perrusi VJ, Arcuri RA, Hassan R, et al. Prevalence of HPV infection in head and neck carcinomas shows geographical variability: a comparative study from Brazil and Germany. Virchows Archiv 2015;466(June (6)):685–93.
Hufbauer M, Akgül B. Molecular mechanisms of human papillomavirus induced skin carcinogenesis. Viruses 2017;9(7):187.
Iftner T, Eberle S, Iftner A, Holz B, Banik N, Quint W, et al. Prevalence of low-risk and high-risk types of human papillomavirus and other risk factors for HPV infection in Germany within different age groups in women up to 30 years of age: an epidemiological observational study. J Med Virol 2010;82(11):1928–39.
International Agency on Research on Cancer (IARC). Human papillomaviruses. IARC Monograohs on the Evaluation of Carcinogenic Risks to Humans. International Agency on Research on Cancer; 2012. p. 255–313.
Introcaso CE, Dunne EF, Hariri S, Panicker G, Unger ER, Markowitz LE. Prevaccine era human papillomavirus types 6, 11, 16 and 18 seropositivity in the U.S.A., National Health and Nutrition Examination Surveys, 2003-2006. Sex Transm Infect 2014;90(6):505–8.
Liu G, Markowitz LE, Hariri S, Panicker G, Unger ER. Seroprevalence of 9 human papillomavirus types in the United States, 2005-2006. J Infect Dis 2016;213 (2):191–8.
Lu B, Viscidi RP, Wu Y, Nyitray AG, Villa LL, Lazcano-Ponce E, et al. Seroprevalence of human papillomavirus (HPV) type 6 and 16 vary by anatomic site of HPV infection in men. Cancer Epidemiol Biomarkers Prev 2012;21(9):1542–6.
Markowitz LE, Sternberg M, Dunne EF, McQuillan G, Unger ER. Seroprevalence of human papillomavirus types 6, 11, 16, and 18 in the United States: National Health and Nutrition Examination Survey 2003-2004. J Infect Dis 2009;200 (7):1059–67.
Michael KM, Waterboer T, Sehr P, Rother A, Reidel U, Boeing H, et al. Seroprevalence of 34 human papillomavirus types in the German general population. PLoS Pathog 2008;4(6)e1000091.
Newall AT, Brotherton JM, Quinn HE, McIntyre PB, Backhouse J, Gilbert L, et al. Population seroprevalence of human papillomavirus types 6, 11, 16, and 18 in men, women, and children in Australia. Clin Infect Dis 2008;46 (11):1647–55.
Petry KU, Luyten A, Justus A, Iftner A, Strehlke S, Reinecke-Luthge A, et al. Prevalence of high-risk HPV types and associated genital diseases in women born in 1988/89 or 1983/84—results of WOLVES, a population-based epidemiological study in Wolfsburg, Germany. BMC Infect Dis 2013;13:135.
Rahman S, Pierce Campbell CM, Rollison DE, Wang W, Waterboer T, Michel A, et al. Seroprevalence and associated factors of 9-valent human papillomavirus (HPV) types among men in the multinational HIM study. PLoS One 2016a;11(11) e0167173.
Rahman S, Pierce Campbell CM, Waterboer T, Rollison DE, Ingles DJ, Torres BN, et al. Seroprevalence of cutaneous human papillomaviruses (HPV) among men in the multinational HIM Study. J Gen Virol 2016b;.
Remschmidt C, Kaufmann AM, Hagemann I, Vartazarova E, Wichmann O, Delere Y. Risk factors for cervical human papillomavirus infection and high-grade intraepithelial lesion in women aged 20 to 31 years in Germany. Int J Gynecol Cancer 2013;23(3):519–26.
Robbins HA, Li Y, Porras C, Pawlita M, Ghosh A, Rodriguez AC, et al. Glutathione S-transferase L1 multiplex serology as a measure of cumulative infection with human papillomavirus. BMC Infect Dis 2014;14:120.
Ryser MD, Rositch A, Gravitt PE. Modeling of US human papillomavirus (HPV) seroprevalence by age and sexual behavior indicates an increasing trend of HPV infection following the sexual revolution. J Infect Dis 2017;216(5):604–11.
Scheidt-Nave C, Kamtsiuris P, Gosswald A, Holling H, Lange M, Busch MA, et al. German health interview and examination survey for adults (DEGS) — design, objectives and implementation of the first data collection wave. BMC Public Health 2012;12:730.
Scherpenisse M, Mollers M, Schepp RM, Boot HJ, de Melker HE, Meijer CJ, et al. Seroprevalence of seven high-risk HPV types in The Netherlands. Vaccine 2012;30(47):6686–93.
Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet 2007;370(9590):890–907.
Schiffman M, Clifford G, Buonaguro FM. Classification of weakly carcinogenic human papillomavirus types: addressing the limits of epidemiology at the borderline. Infect Agent Cancer 2009;4:8.
Thefeld W, Stolzenberg H, Bellach B-M. Bundes-Gesundheitssurvey: Response, Zusammensetzung der Teilnehmer und Non-Responder-Analyse. Gesundheitswesen. Stuttgart: Thieme; 1999. p. 57–S61.
Tiggelaar SM, Lin MJ, Viscidi RP, Ji J, Smith JS. Age-specific human papillomavirus antibody and deoxyribonucleic acid prevalence: a global review. J Adolesc Health 2012;50(2):110–31.
Trottier H, Ferreira S, Thomann P, Costa MC, Sobrinho JS, Prado JC, et al. Human papillomavirus infection and reinfection in adult women: the role of sexual activity and natural immunity. Cancer Res 2010;70(21):8569–77.
Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. Vaccine 2006;24(Suppl. 1):S1–15.
Vaccarella S, Franceschi S, Clifford GM, Touze A, Hsu CC, de Sanjose S, et al. Seroprevalence of antibodies against human papillomavirus (HPV) types 16 and 18 in four continents: the International Agency for Research on Cancer HPV Prevalence Surveys. Cancer Epidemiol Biomarkers Prev 2010;19(9):2379–88.
Van Doorslaer K, Li Z, Xirasagar S, Maes P, Kaminsky D, Liou D, et al. The Papillomavirus Episteme: a major update to the papillomavirus sequence database. Nucleic Acids Res 2017;45(D1):D499–506.
Wang SS, Schiffman M, Shields TS, Herrero R, Hildesheim A, Bratti MC, et al. Seroprevalence of human papillomavirus-16, -18, -31, and -45 in a population-based cohort of 10000 women in Costa Rica. Br J Cancer 2003;89(7):1248–54.
Waterboer T, Sehr P, Michael KM, Franceschi S, Nieland JD, Joos TO, et al. Multiplex human papillomavirus serology based on in situ-purified glutathione s-transferase fusion proteins. Clin Chem 2005;51(10):1845–53.
Wilson L, Pawlita M, Castle PE, Waterboer T, Sahasrabuddhe V, Gravitt PE, et al. Seroprevalence of 8 oncogenic human papillomavirus genotypes and acquired immunity against reinfection. J Infect Dis 2014;210(3):448–55.

Anhang Publikation 2

tropism	mucosal											cutaneous						
risk groups (IARC)	HR									LR								
genus	α											β			γ	μ	ν	
species	α9						α7			α10		α2	β1	β2	β3	γ1	μ1	ν1
type	35	31	33	52	58	16	18	45	39	59	6	11	10	8	38	49	4	1	41
vaccine-relevance		9-val.									9-val.								
						4-val.					4-val.								
						2-val.													

Supplementary Figure 1: Selection criteria of HPV types

Supplementary Table 1. Comparison of GNHIES98 Participants (n = 7,124) with HPV Seroprevalence Study 2016/2017 Participants (n = 6,517) by Weighting Factor-Relevant Variables.

	GNHIES98 participants			HPV seroprevalence study 2016/2017 participants		
Variable	Frequency	Percent non-weighted	Percent weighted	Frequency	Percent non-weighted	Percent weighted
Age						
17-19	267	3.7	3.4	242	3.7	3.4
20-29	1,017	14.3	15.7	916	14.1	15.5
30-39	1,555	21.8	22.5	1,438	22.1	22.7
40-49	1,311	18.4	18.1	1,223	18.8	18.5
50-59	1,359	19.1	16.6	1,260	19.3	16.8
60-69	1,037	14.6	14.2	940	14.4	14.1
70-79	578	8.1	9.4	498	7.6	9.0
Total	7,124	100.0	100.0	6,517	100.0	100.0
Sex						
Male	3,450	48.4	49.2	3,161	48.5	49.4
Female	3,674	51.6	50.8	3,356	51.5	50.6
Total	7,124	100.0	100.0	6,517	100.0	100.0
Migration status						
Migrant	300	4.2	8.7	275	4.2	8.8
Non-migrant	6,824	95.8	91.3	6,242	95.8	91.2
Total	7,124	100.0	100.0	6,517	100.0	100.0
Urbanity (number of residents)						
<2.000	656	9.2	7.4	623	9.6	7.7
2.000 - <5.000	514	7.2	6.9	454	7.0	6.7
5.000 - <20.000	1,116	15.7	15.5	1,021	15.7	15.3
20.000 - <50.000	720	10.1	10.1	657	10.1	10.0
Urban hinterland, 50.000 - <100.000	71	1.0	0.5	68	1.0	0.5
Nucleated town, 50.000 - <100.000	321	4.5	3.9	297	4.6	3.9
Urban hinterland,100.000 - <500.000	487	6.8	5.8	455	7.0	6.0
Nucleated town, 100.000 - <500.000	749	10.5	12.2	706	10.8	12.6
Urban hinterland, >=500.000	607	8.5	9.4	539	8.3	9.2
Nucleated town, >=500.000	1,883	26.4	28.3	1,697	26.0	28.2
Total	7,124	100.0	100.0	6,517	100.0	100.0
West/East/Berlin						
West	4,556	64.0	77.4	4,157	63.8	77.3
East	2,233	31.3	18.5	2,049	31.4	18.5
Berlin	335	4.7	4.2	311	4.8	4.3
Total	7,124	100.0	100.0	6,517	100.0	100.0
Social status (Winkler)						
Low	1,621	23.5	27.8	1,458	23.1	27.4
Middle	3,817	55.4	52.9	3,510	55.6	53.1
high	1,458	21.1	19.4	1,347	21.3	19.6
Total	6,896	100.0	100.0	6,315	100.0	100.0

Supplementary Table 2. Seroprevalence of Individual Cutaneous Human Papillomavirus Types by Sex and Age, HPV seroprevalence study (n = 6,517), 2016/2017 (sera collected 1997-1999).

Group	Subjects, no.	Seroprevalence by HPV type, % (95% CI)						
		1	4	8	10	38	41	49
Overall	**6517**	**34.1 (32.5-35.7) 2211**	**34.7 (33.2-36.3) 2267**	**18.9 (17.8-20.1) 1212**	**11.3 (10.4-12.2) 745**	**10.9 (10.0-11.9) 706**	**8.7 (7.8-9.6) 536**	**11.1 (10.2-12.0) 696**
Females, overall	**3356**	**34.5 (32.7-36.4) 1158**	**33.9 (32.2-35.7) 1140**	**18.3 (16.6-20.0) 604**	**10.9 (9.8-12.1) 370**	**11.1 (9.9-12.6) 366**	**8.7 (7.5-10.0) 270**	**11.5 (10.2-12.9) 368**
Age groups								
18-24	305	46.4 (39.6-53.3) 142	24.6 (19.1-31.1) 79	9.6 (6.4-14.3) 28	4.6 (2.5-8.1) 17	6.8 (4.2-10.9) 21	9.3 (6.0-14.4) 28	6.9 (4.3-10.8) 20
25-29	274	39.3 (32.6-46.4) 106	27.6 (21.8-34.3) 74	9.7 (6.2-14.7) 26	7.2 (4.5-11.3) 20	4.4 (2.6-7.3) 13	9.4 (6.0-14.4) 25	5.8 (3.5-9.6) 16
30-39	729	37.4 (33.3-41.6) 274	31.4 (28.0-35.0) 224	16.7 (13.6-20.3) 110	10.2 (8.0-13.0) 76	8.6 (6.5-11.3) 58	10.3 (8.0-13.2) 65	10.1 (7.9-12.8) 66
40-49	635	37.8 (33.7-42.1) 241	34.0 (29.9-38.3) 218	17.6 (14.7-20.9) 112	11.1 (8.5-14.3) 73	11.7 (9.3-14.4) 75	6.5 (4.4-9.6) 44	11.0 (8.4-14.2) 69
50-59	636	30.2 (25.6-35.2) 182	38.6 (34.6-42.8) 238	22.6 (18.8-26.9) 140	12.5 (10.0-15.6) 78	11.9 (9.2-15.2) 72	9.0 (6.3-12.6) 49	12.9 (9.9-16.5) 75
60-69	492	30.7 (26.8-34.9) 151	40.8 (35.7-46.1) 205	22.7 (18.7-27.2) 119	15.5 (11.9-19.9) 73	14.3 (11.0-18.2) 75	8.7 (5.9-12.8) 37	17.0 (13.3-21.5) 81
70-79	285	21.3 (16.5-27.1) 62	35.7 (29.4-42.5) 102	24.6 (19.0-31.1) 69	11.6 (7.7-17.1) 33	19.2 (14.7-24.7) 52	7.4 (4.3-12.4) 22	14.0 (9.9-19.5) 41
Males, overall	**3161**	**33.6 (31.4-36.0) 1053**	**35.6 (33.4-37.8) 1127**	**19.6 (18.1-21.2) 608**	**11.7 (10.3-13.2) 375**	**10.7 (9.5-12.0) 340**	**8.7 (7.6-9.8) 266**	**10.7 (9.6-12.0) 328**
Age groups								
18-24	342	39.8 (33.3-46.8) 131	32.4 (26.8-38.6) 110	12.6 (8.6-18.1) 37	7.2 (4.6-10.9) 23	8.5 (5.8-12.3) 26	7.7 (5.0-11.6) 22	8.5 (5.6-12.7) 25
25-29	237	35.7 (28.7-43.4) 88	29.3 (22.7-37.0) 72	10.0 (6.2-15.8) 22	9.5 (5.9-14.9) 25	7.5 (4.2-13.1) 16	6.9 (4.2-11.1) 20	6.5 (3.7-11.3) 17
30-39	709	38.1 (34.2-42.1) 272	38.3 (34.6-42.3) 274	14.4 (11.6-17.7) 98	12.1 (9.4-15.4) 85	9.5 (7.3-12.4) 68	9.7 (7.2-13.0) 61	9.9 (7.7-12.7) 70
40-49	588	33.6 (29.0-38.5) 198	38.6 (34.0-43.4) 216	21.1 (17.2-25.6) 116	10.8 (8.0-14.3) 60	9.7 (7.3-12.7) 58	8.0 (5.9-10.8) 47	11.3 (8.3-15.2) 58
50-59	624	29.5 (25.1-34.2) 184	37.8 (33.3-42.6) 237	24.8 (21.7-28.2) 154	12.4 (10.1-15.2) 80	12.2 (9.4-15.6) 76	9.5 (7.2-12.5) 59	10.7 (8.5-13.4) 71
60-69	448	28.6 (24.0-33.7) 126	31.6 (26.7-37.0) 146	27.4 (22.4-33.2) 118	13.5 (10.0-17.8) 65	15.5 (11.8-20.1) 72	8.9 (6.3-12.5) 40	14.2 (11.0-18.1) 59
70-79	213	26.6 (19.8-34.7) 54	32.2 (25.8-39.3) 72	28.1 (21.7-35.4) 63	16.7 (11.6-23.5) 37	12.1 (8.1-17.6) 24	8.1 (4.4-14.4) 17	14.1 (9.6-20.2) 28

Note. CI, confidence interval.

Supplementary Table 3. Multiple Seropositivity of Low Risk (6, 11) and High Risk HPV Types (16, 18, 31, 33, 35, 39, 45, 52, 58, 59) by Sex, HPV Seroprevalence Study (n = 6,517), 2016/2017 (sera collected 1997-1999).

	Number of HPV types	Overall, % (95% CI), No.	Female, % (95% CI), No.	Male, % (95% CI), No.
Low risk HPV types	0	86.7 (85.6-87.7) 5655	85.4 (84.0-86.8) 2862	88.0 (86.6-89.2) 2793
	1	10.6 (9.8-11.4) 689	11.5 (10.4-12.8) 388	9.6 (8.5-10.8) 301
	2	2.7 (2.3-3.3) 173	3.1 (2.5-3.7) 106	2.4 (1.8-3.3) 67
High risk HPV types	0	72.1 (70.6-73.6) 4,685	70.7 (68.6-72.7) 2,362	73.6 (71.7-75.5) 2,323
	1	18.4 (17.3-19.6) 1,210	19.1 (17.5-20.8) 645	17.7 (16.3-19.3) 565
	2	4.9 (4.3-5.5) 320	4.9 (4.1-5.9) 166	4.8 (4.0-5.8) 154
	>=3	4.6 (4.0-5.3) 302	5.3 (4.5-6.3) 183	3.8 (3.1-4.7) 119

Supplementary Table 4. Factors Associated with Seropositivity to Human Papillomavirus (HPV) Type 6 in Females and Males, HPV Seroprevalence Study, 2016/2017 (sera collected 1997-1999).

	Females		Males	
Variable	Crude PR (95%CI)	Fully aPR (95%CI)$	Crude PR (95%CI)	Fully aPR (95%CI)$
Age groups (y)				
18-24	Reference	Reference	Reference	Reference
25-29	1.67 (0.93-3.02)	1.65 (0.88-3.12)	0.72 (0.42-1.21)	0.63 (0.37-1.08)
30-39	**1.71 (1.05-2.79)**	1.56 (0.92-2.64)	1.15 (0.74-1.77)	1.00 (0.65-1.54)
40-49	**1.89 (1.15-3.09)**	**1.80 (1.08-3.02)**	1.24 (0.84-1.82)	1.09 (0.74-1.61)
50-59	1.23 (0.73-2.09)	1.27 (0.73-2.20)	**0.59 (0.37-0.95)**	**0.50 (0.32-0.80)**
60-69	**1.70 (1.02-2.84)**	**1.85 (1.09-3.14)**	**0.59 (0.35-1.00)**	**0.53 (0.31-0.91)**
70-79	0.90 (0.50-1.61)	0.98 (0.53-1.82)	**0.46 (0.24-0.89)**	**0.39 (0.20-0.80)**
Region of residence I				
East	Reference	na*	Reference	na*
West	0.98 (0.81-1.18)	na*	1.18 (0.94-1.48)	na*
Region of residence II				
Northern Germany	Reference	na*	Reference	na*
Central Germany	0.99 (0.79-1.25)	na*	1.13 (0.89-1.42)	na*
Southern Germany	0.97 (0.73-1.29)	na*	1.11 (0.86-1.45)	na*
Country of birth				
Germany	Reference	na*	Reference	Reference
Other	1.07 (0.74-1.54)	na*	**1.68 (1.21-2.34)**	**1.59 (1.17-2.17)**
Urbanity				
Rural	Reference	na*	Reference	Reference
Small city	1.25 (0.93-1.67)	na*	0.98 (0.75-1.29)	0.99 (0.75-1.29)
Medium sized city	1.02 (0.79-1.33)	na*	**1.31 (1.01-1.71)**	**1.32 (1.01-1.71)**
Large city	1.08 (0.86-1.35)	na*	0.96 (0.75-1.22)	0.97 (0.79-1.21)
History of smoking				
No	Reference	Reference	Reference	Reference
Yes	**1.49 (1.21-1.83)**	**1.29 (1.01-1.64)**	**1.65 (1.27-2.16)**	**1.61 (1.24-2.11)**
Education				
Low	1.01 (0.81-1.27)	na*	1.12 (0.76-1.65)	na*
Middle	Reference	na*	Reference	na*
High	1.07 (0.79-1.43)	na*	0.87 (0.66-1.14)	na*
Seropositive for any other STI				
No	Reference	Reference	Reference	Reference
Yes	**1.59 (1.30-1.95)**	**1.49 (1.20-1.86)**	**1.59 (1.22-2.07)**	**1.47 (1.13-1.91)**
Lifetime no. of sex partners				
0	0.20 (0.03-1.48)	0.30 (0.04-2.25)	1.27 (0.42-3.84)	na*
1	Reference	Reference	Reference	na*
2-4	1.04 (0.78-1.38)	0.93 (0.70-1.25)	0.93 (0.58-1.49)	
5-9	**1.79 (1.27-2.53)**	1.41 (0.96-2.07)	1.18 (0.75-1.86)	na*
>=10	1.57 (0.99-2.49)	1.16 (0.70-1.93)	1.19 (0.79-1.77)	na*
NA	1.11 (0.81-1.51)	0.97 (0.70-1.34)	1.29 (0.94-1.77)	na*
History of use of oral contraceptives				
No	Reference	na*	--	--
Yes	1.09 (0.87-1.36)	na*	--	--

Abbreviations: aPR, adjusted prevalence ratio; CI, confidence interval; na, not available; STI, sexually transmitted infection

na* variables were not significantly associated with HPV seroprevalence in the univariable model and therefore not included in the fully adjusted model

$ the aPR are adjusted for all variables which are listed in the table and remained in the final model

Statistically significant PR are shown in **bold font**

Supplementary Table 5. Factors Associated with Seropositivity to Human Papillomavirus (HPV) Type 11 in Females and Males, HPV Seroprevalence Study, 2016/2017 (sera collected 1997-1999).

	Females		Males	
Variable	Crude PR (95%CI)	Fully aPR (95%CI)[$]	Crude PR (95%CI)	Fully aPR (95%CI)[$]
Age groups (y)				
18-24	Reference	Reference	Reference	na*
25-29	2.01 (0.68-5.96)	1.48 (0.48-4.59)	0.23 (0.04-1.20)	na*
30-39	2.20 (0.96-5.03)	1.66 (0.74-3.72)	1.40 (0.67-2.94)	na*
40-49	**2.43 (1.08-5.48)**	1.86 (0.82-4.23)	1.07 (0.55-2.09)	na*
50-59	1.89 (0.81-4.39)	1.68 (0.73-3.88)	0.65 (0.28-1.51)	na*
60-69	**2.52 (1.08-5.89)**	**2.58 (1.07-6.26)**	0.79 (0.33-1.91)	na*
70-79	2.51 (0.96-6.57)	2.53 (0.90-7.06)	0.63 (0.25-1.55)	na*
Region of residence I				
East	Reference	na*	Reference	Reference
West	0.85 (0.59-1.22)	na*	**1.90 (1.16-3.10)**	**1.81 (1.11-2.94)**
Region of residence II				
Northern Germany	Reference	na*	Reference	na*
Central Germany	1.03 (0.64-1.65)	na*	1.28 (0.72-2.29)	na*
Southern Germany	0.78 (0.45-1.36)	na*	0.74 (0.39-1.40)	na*
Country of birth				
Germany	Reference	na*	Reference	na*
Other	1.02 (0.56-1.84)	na*	1.56 (0.81-3.01)	na*
Urbanity				
Rural	Reference	na*	Reference	Reference
Small city	0.97 (0.59-1.57)	na*	1.48 (0.65-3.39)	1.36 (0.59-3.16)
Medium sized city	0.90 (0.55-1.48)	na*	**2.67 (1.24-5.74)**	**2.34 (1.09-5.01)**
Large city	1.46 (0.96-2.21)	na*	**3.21 (1.57-6.58)**	**2.74 (1.32-5.68)**
History of smoking				
No	Reference	Reference	Reference	na*
Yes	**1.59 (1.11-2.28)**	1.48 (0.95-2.32)	1.54 (0.97-2.46)	na*
Education				
Low	1.35 (0.86-2.11)	na*	1.15 (0.58-2.27)	na*
Middle	Reference	na*	Reference	na*
High	1.26 (0.79-2.02)	na*	1.26 (0.75-2.10)	na*
Seropositive for any other STI				
No	Reference	Reference	Reference	Reference
Yes	**2.78 (1.83-4.24)**	**2.57 (1.62-4.07)**	**2.45 (1.28-4.71)**	**2.30 (1.19-4.45)**
Lifetime no. of sex partners				
0	no[+]	no[+]	1.45 (0.18-11.94)	1.33 (0.16-11.12)
1	Reference	Reference	Reference	Reference
2-4	0.79 (0.50-1.26)	0.69 (0.42-1.14)	1.62 (0.56-4.65)	1.48 (0.53-4.15)
5-9	1.56 (0.80-3.02)	1.16 (0.57-2.35)	2.84 (0.98-8.17)	2.49 (0.90-6.90)
>=10	1.67 (0.76-3.69)	1.18 (0.50-2.76)	**2.86 (1.30-6.31)**	**2.29 (1.06-4.92)**
NA	0.82 (0.48-1.39)	0.61 (0.34-1.09)	2.03 (0.91-4.52)	1.86 (0.85-4.10)
History of use of oral contraceptives				
No	Reference	na*	--	--
Yes	1.16 (0.74-1.82)	na*	--	--

Abbreviations: aPR, adjusted prevalence ratio; CI, confidence interval; na, not available; STI, sexually transmitted infection

na* variables were not significantly associated with HPV seroprevalence in the univariable model and therefore not included in the fully adjusted model

no[+] no observations in categories

$ the aPR are adjusted for all variables which are listed in the table and remained in the final model

Statistically significant PR are shown in **bold font**

Supplementary Table 6. Factors Associated with Seropositivity to Human Papillomavirus (HPV) Type 18 in Females and Males, HPV Seroprevalence Study, 2016/2017 (sera collected 1997-1999).

	Females		Males	
Variable	Crude PR (95%CI)	Fully aPR (95%CI)[$]	Crude PR (95%CI)	Fully aPR (95%CI)[$]
Age groups (y)				
18-24	Reference	na*	Reference	na*
25-29	1.29 (0.59-2.83)	na*	1.14 (0.56-2.30)	na*
30-39	1.45 (0.77-2.73)	na*	1.13 (0.59-2.16)	na*
40-49	1.69 (0.90-3.16)	na*	1.04 (0.51-2.11)	na*
50-59	1.23 (0.60-2.55)	na*	1.31 (0.74-2.31)	na*
60-69	1.71 (0.86-3.39)	na*	1.10 (0.56-2.17)	na*
70-79	1.45 (0.72-2.91)	na*	1.17 (0.51-2.68)	na*
Region of residence I				
East	Reference	na*	Reference	na*
West	0.93 (0.71-1.23)	na*	1.10 (0.76-1.60)	na*
Region of residence II				
Northern Germany	Reference	na*	Reference	Reference
Central Germany	0.99 (0.66-1.47)	na*	**1.68 (1.01-2.81)**	1.67 (1.00-2.80)
Southern Germany	1.05 (0.69-1.59)	na*	0.98 (0.56-1.72)	0.98 (0.56-1.71)
Country of birth				
Germany	Reference	na*	Reference	na*
Other	1.48 (0.98-2.25)	na*	0.82 (0.40-1.68)	na*
Urbanity				
Rural	Reference	Reference	Reference	na*
Small city	1.04 (0.69-1.57)	1.08 (0.71-1.66)	0.68 (0.40-1.16)	na*
Medium sized city	**1.59 (1.11-2.26)**	**1.65 (1.14-2.38)**	0.93 (0.55-1.57)	na*
Large city	1.36 (0.91-2.03)	1.25 (0.83-1.90)	1.30 (0.78-2.19)	na*
History of smoking				
No	Reference	na*	Reference	na*
Yes	0.96 (0.72-1.28)	na*	0.94 (0.66-1.33)	na*
Education				
Low	1.39 (1.00-1.94)	1.36 (0.97-1.90)	0.98 (0.54-1.76)	na*
Middle	Reference	Reference	Reference	na*
High	**1.40 (1.01-1.95)**	1.34 (0.96-1.87)	1.04 (0.74-1.46)	na*
Seropositive for any other STI				
No	Reference	Reference	Reference	Reference
Yes	**2.11 (1.47-3.02)**	**2.02 (1.40-2.92)**	**1.69 (1.16-2.45)**	**1.64 (1.14-2.35)**
Lifetime no. of sex partners				
0	1.19 (0.18-7.77)	0.30 (0.04-2.25)	**4.99 (1.95-12.78)**	**5.06 (1.96-13.06)**
1	Reference	Reference	Reference	Reference
2-4	0.88 (0.59-1.34)	0.93 (0.70-1.25)	1.82 (0.94-3.52)	1.76 (0.93-3.34)
5-9	1.54 (0.91-2.58)	1.41 (0.96-2.07)	1.44 (0.61-3.40)	1.41 (0.62-3.20)
>=10	**1.84 (1.01-3.36)**	1.16 (0.70-1.93)	1.36 (0.67-2.78)	1.27 (0.63-2.55)
NA	1.35 (0.90-2.02)	0.97 (0.70-1.34)	1.67 (0.88-3.17)	1.61 (0.86-3.00)
History of use of oral contraceptives				
No	Reference	na*	--	--
Yes	1.17 (0.86-1.60)	na*	--	--

Abbreviations: aPR, adjusted prevalence ratio; CI, confidence interval; na, not available; STI, sexually transmitted infection

na* variables were not significantly associated with HPV seroprevalence in the univariable model and therefore not included in the fully adjusted model

$ the aPR are adjusted for all variables which are listed in the table and remained in the final model

Statistically significant PR are shown in **bold font**

Supplementary Table 7. Factors Associated with Seropositivity to at least one of high-risk Human Papillomavirus (HPV) Types 16, 18, 31, 33, 35, 39, 45, 52, 58 or 59 in Females and Males, HPV Seroprevalence Study, 2016/2017 (sera collected 1997-1999).

	Females		Males	
Variable	Crude PR (95%CI)	Fully aPR (95%CI)[$]	Crude PR (95%CI)	Fully aPR (95%CI)[$]
Age groups (y)				
18-24	Reference	Reference	Reference	Reference
25-29	1.25 (0.89-1.76)	1.19 (0.84-1.68)	**1.46 (1.09-1.95)**	**1.42 (1.06-1.91)**
30-39	**1.38 (1.06-1.80)**	1.29 (0.98-1.69)	**1.32 (1.02-1.71)**	1.24 (0.95-1.62)
40-49	**1.36 (1.08-1.72)**	1.25 (0.98-1.61)	1.26 (0.99-1.62)	1.17 (0.90-1.51)
50-59	**1.31 (1.02-1.69)**	1.24 (0.94-1.62)	**1.47 (1.15-1.87)**	**1.39 (1.07-1.80)**
60-69	**1.36 (1.05-1.76)**	1.28 (0.97-1.70)	**1.46 (1.16-1.85)**	**1.38 (1.07-1.77)**
70-79	1.20 (0.87-1.66)	1.09 (0.77-1.55)	**1.45 (1.08-1.96)**	1.37 (1.00-1.88)
Region of residence I				
East	Reference	na*	Reference	na*
West	0.91 (0.79-1.05)	na*	1.00 (0.85-1.16)	na*
Region of residence II				
Northern Germany	Reference	na*	Reference	na*
Central Germany	1.07 (0.88-1.30)	na*	1.15 (0.98-1.34)	na*
Southern Germany	1.05 (0.86-1.28)	na*	0.91 (0.74-1.11)	na*
Country of birth				
Germany	Reference	na*	Reference	na*
Other	1.12 (0.90-1.38)	na*	0.90 (0.71-1.15)	na*
Urbanity				
Rural	Reference	na*	Reference	na*
Small city	1.01 (0.81-1.26)	na*	1.04 (0.83-1.31)	na*
Medium sized city	1.10 (0.90-1.36)	na*	1.06 (0.86-1.31)	na*
Large city	1.12 (0.93-1.35)	na*	0.98 (0.79-1.22)	na*
History of smoking				
No	Reference	na*	Reference	na*
Yes	1.04 (0.92-1.17)	na*	0.94 (0.81-1.09)	na*
Education				
Low	1.08 (0.95-1.23)	na*	0.82 (0.66-1.03)	na*
Middle	Reference	na*	Reference	na*
High	0.99 (0.85-1.16)	na*	1.01 (0.89-1.16)	na*
Seropositive for any other STI				
No	Reference	Reference	Reference	Reference
Yes	**1.54 (1.36-1.75)**	**1.49 (1.31-1.70)**	**1.49 (1.30-1.71)**	**1.47 (1.28-1.69)**
Lifetime no. of sex partners				
0	1.07 (0.51-2.23)	1.40 (0.66-2.96)	1.14 (0.62-2.11)	1.17 (0.64-2.15)
1	Reference	Reference	Reference	Reference
2-4	1.18 (0.98-1.43)	1.14 (0.94-1.38)	1.16 (0.89-1.52)	1.15 (0.88-1.49)
5-9	**1.43 (1.12-1.81)**	**1.28 (1.01-1.63)**	1.18 (0.90-1.56)	1.16 (0.88-1.53)
>=10	**1.47 (1.09-2.00)**	1.28 (0.93-1.75)	1.27 (0.96-1.67)	1.18 (0.90-1.55)
NA	**1.28 (1.05-1.55)**	1.20 (0.99-1.45)	**1.29 (1.01-1.64)**	1.21 (0.95-1.53)
History of use of oral contraceptives				
No	Reference	na*	--	--
Yes	0.99 (0.85-1.14)	na*	--	--

Abbreviations: aPR, adjusted prevalence ratio; CI, confidence interval; na, not available; STI, sexually transmitted infection

na* variables were not significantly associated with HPV seroprevalence in the univariable model and therefore not included in the fully adjusted model

$ the aPR are adjusted for all variables which are listed in the table and remained in the final model

Statistically significant PR are shown in **bold font**

Supplementary Table 8. Factors Associated with Seropositivity to at least one of low-risk Human Papillomavirus (HPV) Types 6 or 11 in Females and Males, HPV Seroprevalence Study, 2016/2017 (sera collected 1997-1999).

	Females		Males	
Variable	Crude PR (95%CI)	Fully aPR (95%CI)[$]	Crude PR (95%CI)	Fully aPR (95%CI)[$]
Age groups (y)				
18-24	Reference	Reference	Reference	Reference
25-29	1.66 (0.93-2.96)	1.60 (0.86-2.97)	**0.66 (0.39-1.10)**	**0.57 (0.33-0.96)**
30-39	**1.87 (1.17-2.99)**	**1.67 (1.01-2.75)**	**1.15 (0.78-1.69)**	0.95 (0.64-1.42)
40-49	**2.08 (1.29-3.36)**	**1.95 (1.19-3.20)**	1.16 (0.81-1.68)	0.99 (0.67-1.46)
50-59	**1.39 (0.85-2.28)**	1.40 (0.83-2.34)	**0.60 (0.40-0.91)**	**0.48 (0.31-0.75)**
60-69	**1.87 (1.14-3.06)**	**1.99 (1.19-3.35)**	**0.61 (0.38-1.00)**	**0.52 (0.31-0.87)**
70-79	1.24 (0.69-2.24)	1.35 (0.72-2.51)	**0.49 (0.27-0.88)**	**0.39 (0.21-0.72)**
Region of residence I				
East	Reference	na*	Reference	na*
West	0.95 (0.80-1.13)	na*	1.21 (0.97-1.50)	na*
Region of residence II				
Northern Germany	Reference	na*	Reference	na*
Central Germany	0.99 (0.78-1.26)	na*	1.07 (0.86-1.34)	na*
Southern Germany	0.95 (0.71-1.28)	na*	1.03 (0.80-1.33)	na*
Country of birth				
Germany	Reference	na*	Reference	Reference
Other	1.03 (0.75-1.43)	na*	**1.53 (1.11-2.11)**	**1.39 (1.03-1.87)**
Urbanity				
Rural	Reference	na*	Reference	Reference
Small city	1.20 (0.90-1.61)	na*	1.01 (0.78-1.31)	1.03 (0.79-1.33)
Medium sized city	1.03 (0.79-1.35)	na*	**1.37 (1.05-1.78)**	**1.41 (1.08-1.83)**
Large city	1.18 (0.92-1.51)	na*	1.08 (0.86-1.37)	1.13 (0.91-1.41)
History of smoking				
No	Reference	Reference	Reference	Reference
Yes	**1.46 (1.20-1.78)**	**1.30 (1.03-1.64)**	**1.64 (1.27-2.13)**	**1.63 (1.24-2.12)**
Education				
Low	1.10 (0.88-1.37)	na*	1.15 (0.81-1.63)	na*
Middle	Reference	na*	Reference	na*
High	1.13 (0.87-1.48)	na*	0.94 (0.72-1.23)	na*
Seropositive for any other STI				
No	Reference	Reference	Reference	Reference
Yes	**1.72 (1.43-2.06)**	**1.60 (1.30-1.96)**	**1.69 (1.31-2.17)**	**1.55 (1.21-1.98)**
Lifetime no. of sex partners				
0	0.16 (0.02-1.21)	0.27 (0.04-2.01)	1.26 (0.42-3.82)	1.40 (0.48-4.03)
1	Reference	Reference	Reference	Reference
2-4	0.92 (0.70-1.20)	0.82 (0.63-1.08)	0.97 (0.61-1.54)	0.83 (0.54-1.27)
5-9	**1.57 (1.10-2.24)**	1.24 (0.84-1.82)	1.24 (0.78-1.96)	1.00 (0.65-1.53)
>=10	**1.57 (1.02-2.41)**	1.16 (0.74-1.83)	1.40 (0.95-2.05)	1.05 (0.74-1.47)
NA	**1.04 (0.78-1.39)**	0.88 (0.65-1.20)	**1.38 (1.01-1.90)**	1.16 (0.85-1.58)
History of use of oral contraceptives				
No	Reference	na*	--	--
Yes	1.03 (0.84-1.27)	na*	--	--

Abbreviations: aPR, adjusted prevalence ratio; CI, confidence interval; na, not available; STI, sexually transmitted infection

na* variables were not significantly associated with HPV seroprevalence in the univariable model and therefore not included in the fully adjusted model

$ the aPR are adjusted for all variables which are listed in the table and remained in the final model

Statistically significant PR are shown in **bold font**

5.3. PUBLIKATION 3

Loenenbach, A., Pawlita, M., Waterboer, T., Harder T., Poethko-Müller, C., Thamm, M., Lachmann, R., Deleré, Y., Wichmann, O., Wiese-Posselt, M. Seroprevalence of mucosal and cutaneous Human Papillomavirus (HPV) types among children and adolescents in the general population in Germany. BMC Inf Dis, 2022. doi: 10.1186/s12879-022-07028-8. Journal Impact Factor: 3,090; Journal Citation Reports; Jahr „2020"; Ausgewählte Kategorie „Infectious Diseases".

Journal Data Filtered By: **Selected JCR Year: 2020** Selected Editions: SCIE,SSCI
Selected Categories: **"INFECTIOUS DISEASES"** Selected Category
Scheme: WoS
Gesamtanzahl: 92 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	LANCET INFECTIOUS DISEASES	42,483	25.071	0.070070
2	Lancet HIV	5,368	12.767	0.022020
3	CLINICAL INFECTIOUS DISEASES	89,276	9.079	0.113210
4	JOURNAL OF TRAVEL MEDICINE	5,260	8.490	0.004900
5	CLINICAL MICROBIOLOGY AND INFECTION	24,871	8.067	0.031710
6	Emerging Microbes & Infections	8,988	7.163	0.012560
7	EMERGING INFECTIOUS DISEASES	44,051	6.883	0.049780
8	Eurosurveillance	15,123	6.307	0.023830
9	Travel Medicine and Infectious Disease	5,034	6.211	0.003430
10	JOURNAL OF INFECTION	15,496	6.072	0.012570
11	INFECTIOUS DISEASE CLINICS OF NORTH AMERICA	4,090	5.982	0.006870
12	Virulence	5,784	5.882	0.007420
13	INTERNATIONAL JOURNAL OF HYGIENE AND ENVIRONMENTAL HEALTH	7,425	5.840	0.008110
14	JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY	38,715	5.790	0.042490
15	Journal of the International AIDS Society	6,474	5.396	0.017390
16	Infectious Diseases and Therapy	1,331	5.322	0.003260
17	INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS	20,409	5.283	0.015470

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
18	JOURNAL OF INFECTIOUS DISEASES	54,782	5.226	0.066740
19	Expert Review of Anti-Infective Therapy	5,263	5.091	0.006190
20	ACS Infectious Diseases	3,865	5.084	0.009140
21	AIDS PATIENT CARE AND STDS	4,231	5.078	0.005410
22	Current HIV/AIDS Reports	2,188	5.071	0.004750
23	Transboundary and Emerging Diseases	7,104	5.005	0.010830
24	CURRENT OPINION IN INFECTIOUS DISEASES	4,522	4.915	0.006290
25	Antimicrobial Resistance and Infection Control	3,629	4.887	0.008170
26	Antibiotics-Basel	3,730	4.639	0.004640
27	Infectious Diseases of Poverty	3,434	4.520	0.006920
28	JOURNAL OF MICROBIOLOGY IMMUNOLOGY AND INFECTION	4,936	4.399	0.005200
29	Epidemics	1,395	4.396	0.004420
30	Influenza and Other Respiratory Viruses	3,470	4.380	0.006270
31	Current Opinion in HIV and AIDS	3,006	4.283	0.007440
32	AIDS	20,317	4.177	0.029400
33	MEDICAL MYCOLOGY	6,503	4.076	0.005900
34	Journal of Global Antimicrobial Resistance	2,904	4.035	0.005030
35	Infection and Drug Resistance	3,973	4.003	0.007410
36	JOURNAL OF HOSPITAL INFECTION	12,760	3.926	0.011240
37	Open Forum Infectious Diseases	6,969	3.835	0.024460
38	One Health	829	3.800	0.001560

Selected JCR Year: 2020; Selected Categories: "INFECTIOUS DISEASES"

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
39	Ticks and Tick-Borne Diseases	4,726	3.744	0.006820
40	JAIDS-JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES	15,629	3.731	0.027620
41	JOURNAL OF VIRAL HEPATITIS	5,219	3.728	0.009080
42	Current Infectious Disease Reports	1,737	3.725	0.003160
43	Journal of Infection and Public Health	3,870	3.718	0.006030
44	Journal of Virus Eradication	720	3.696	0.002710
45	INTERNATIONAL JOURNAL OF INFECTIOUS DISEASES	17,784	3.623	0.018060
46	INFECTION	5,278	3.553	0.005740
47	SEXUALLY TRANSMITTED INFECTIONS	5,335	3.519	0.008190
48	INFECTION AND IMMUNITY	50,234	3.441	0.018510
49	Microbial Drug Resistance	4,168	3.431	0.004950
50	Infectious Diseases	1,772	3.404	0.004020
51	INFECTION GENETICS AND EVOLUTION	11,716	3.342	0.014980
52	EUROPEAN JOURNAL OF CLINICAL MICROBIOLOGY & INFECTIOUS DISEASES	11,581	3.267	0.012960
53	INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY	12,884	3.254	0.015830
54	HIV MEDICINE	2,926	3.180	0.005440
55	Pathogens and Disease	2,424	3.166	0.004360
56	Journal of the Pediatric Infectious Diseases Society	1,986	3.164	0.005610
57	BMC INFECTIOUS DISEASES	24,042	3.090	0.044520

Selected JCR Year: 2020; Selected Categories: "INFECTIOUS DISEASES"

Loenenbach *et al. BMC Infectious Diseases* (2022) 22:44
https://doi.org/10.1186/s12879-022-07028-8

BMC Infectious Diseases

RESEARCH Open Access

Seroprevalence of mucosal and cutaneous human papillomavirus (HPV) types among children and adolescents in the general population in Germany

Anna Loenenbach[1,2*], Michael Pawlita[3], Tim Waterboer[3], Thomas Harder[1], Christina Poethko-Müller[4], Michael Thamm[4], Raskit Lachmann[1], Yvonne Deleré[5], Ole Wichmann[1] and Miriam Wiese-Posselt[1,6]

Abstract

Background: In Germany, HPV vaccination of adolescent girls was introduced in 2007. Nationally representative data on the distribution of vaccine-relevant HPV types in the pre-vaccination era are, however, only available for the adult population. To obtain data in children and adolescents, we assessed the prevalence and determinants of serological response to 16 different HPV types in a representative sample of 12,257 boys and girls aged 1–17 years living in Germany in 2003–2005.

Methods: Serum samples were tested for antibodies to nine mucosal and seven cutaneous HPV types. The samples had been collected during the nationally representative German Health Interview and Examination Survey for Children and Adolescents in 2003–2006. We calculated age- and gender-specific HPV seroprevalence. We used multivariable regression models to identify associations between demographic and behavioral characteristics and HPV seropositivity.

Results: We found low but non-zero seroprevalence for the majority of tested HPV types among children and adolescents in Germany. The overall seroprevalence of HPV-16 was 2.6%, with slightly higher values in adolescents. Seroprevalence of all mucosal types but HPV-6 ranged from 0.6% for HPV-33, to 6.4% for HPV-31 and did not differ by gender. We found high overall seroprevalence for HPV-6 with 24.8%. Cutaneous HPV type seroprevalence ranged from 4.0% for HPV-38 to 31.7% for HPV-1. In the majority of cutaneous types, seroprevalence did not differ between boys and girls, but increased sharply with age, (e.g., HPV-1 from 1.5% in 1–3-years-old to 45.1% in 10–11-years-old). Associations between behavioral factors and type-specific HPV prevalence were determined to be heterogeneous.

Conclusions: We report the first nationally representative data of naturally acquired HPV antibody reactivity in the pre-HPV-vaccination era among children and adolescents living in Germany. These data can be used as baseline estimates for evaluating the impact of the current HPV vaccination strategy targeting 9–14-years-old boys and girls.

Keywords: Human papillomavirus, Seroprevalence, Risk factors, Children, Adolescents, Germany

Background

Infections with human papillomaviruses (HPVs) are among the most common sexually transmitted infections but can also be transmitted perinatally. HPV belongs to the diverse Papillomaviridae virus family and comprises

*Correspondence: LoenenbachA@rki.de
[1] Department for Infectious Disease Epidemiology, Immunization Unit, Robert Koch-Institute, Berlin, Germany
Full list of author information is available at the end of the article

over 200 different types, which can be further categorized based on different parameters [1–3]. HPV types belong to different genera and species based on their phylogenetic relationship [4]. They can also be categorized into two tropism groups, comprising cutaneous HPV types (cutHPV) and mucosal types (mucHPV). Only a small fraction of mucHPV belonging to the alpha genus, like HPV-16 and HPV-18, are assigned to the so-called high-risk (HR) group, due to their role as causative agents of various types of precancerous lesions and cancer [5, 6]. However, the majority of HPV-infected persons develop no visible signs or symptoms, and infections are usually transient and cleared within 12–24 months [5, 7–9]. Infections with other HPV types can lead to different clinical manifestations. The so-called low-risk (LR) types HPV-6 and HPV-11 can cause external benign genital warts [6]. CutHPV, e.g. HPV-1 or HPV-4, are usually found on healthy skin [10], even though they can also be detected in skin lesions such as benign skin warts [4, 6], and some types have been discussed to be involved in skin carcinogenesis [11].

Children and adolescents before sexual debut can also be affected by HPV infections. Typical disease manifestations of HPV infection in children are skin warts [12], commonly transmitted by cutHPV infections [13]. Skin warts are mainly caused by HPV types 1, 2, 3, 4, 27 and 57 [3]. There are different types of warts, including common warts (verruca vulgaris), plantar warts (myrmecias) and flat warts (verruca plana) with different prevalence and age distributions, which could be due to differences in transmission modes [3, 14]. Generally, HPV associated skin warts are rare in preschool children, and peak among children aged 10–14 years, followed by a rapid decline at 20 years of age with no difference between girls and boys [3]. Other rare diseases caused by HPV infections in children and adolescents are juvenile-onset recurrent respiratory papillomatosis (JoRRP), oral papilloma or anogenital warts [15]. JoRRP is most prevalent among children under five, mainly caused by persistent HPV-6 and HPV-11 infections and associated with maternal transmission [15]. However, there is also growing evidence of HR-HPV infections in healthy children [3, 16].

There are only few HPV serology data in children available, even though research on HPV infections in children already started more than 50 years ago [17–19]. Research primarily focused on modes of HPV transmission such as perinatal mother-infant transmission [16] or prevalence among adolescents related to the start of sexual activities. Study results on risk of vertical transmission vary [20, 21] and the exact routes remain unclear [22]. Nevertheless, detection of genital HR-HPV DNA in infants has been repeatedly reported by various studies [21, 23, 24]. Next to perinatal transmission, alternative routes were addressed, such as periconceptual, antenatal, via amniotic fluid [22]. HPV infections can be also horizontally transmitted via autoinoculation, heteroinoculation or via fomites [3, 25, 26]. HPV infections leading to anogenital warts in children are also discussed as a result of sexual transmission in the context of sexual abuse [14, 27]. Anogenital warts, based on vertical or sexual transmission are mainly due to mucHPV 6, 11, 16 und 18 [3, 27]. Anogenital warts due to cutHPV 1, 2, 3 or 4 can be due to hetero- or autoinoculation [3]. It is important to notice, however, that the exact transmission routes in infants and children remain controversial [3, 26, 28], which makes it even more relevant to evaluate age-specific prevalence data in this population.

To investigate the prevalence of HPV infections, DNA testing is used as the reference standard for the detection of current HPV infections [29]. While DNA testing is not an appropriate method to assess previous infections [30], testing for HPV-specific antibodies in an unvaccinated population provides information about past HPV exposure [30, 31]. HPV serology has been established as an important method for population-based studies focusing on type-specific cumulative lifetime exposure to HPV. However, there are only few seroprevalence studies that focus on children [16, 32–34].

Our study aimed to determine age-specific HPV seroprevalence in a representative sample of 12,257 boys and girls aged 1–17 years living in Germany in the years 2003 to 2005. As HPV vaccination of girls has only been introduced in Germany in 2007, our results show naturally acquired antibody reactivity in the pre-HPV vaccination era.

Methods

Study population

Archived serum samples were obtained from the German Health Survey for Children and Adolescents (KiGGS) carried out by the Robert Koch Institute (RKI) from 2003 to 2006 [35]. This cross-sectional health survey was the baseline study of the RKI health monitoring program and aimed to collect and analyze nation-wide representative data on the health status of children and adolescents in Germany aged 0–17 years [36]. Recruitment was based on a two-stage stratified cluster sampling design, with participants randomly selected from the population registers of 167 cities in Germany (for a detailed description of the study design, see [36, 37]). The overall response rate was 66.6% [36].

The study was conducted according to the Federal and State Commissioners for Data Protection guidelines and was approved by the Charité University Medicine Berlin ethics committee and the Federal Commissioner for Data

Protection. Informed written consent and agreement were obtained from the parents of all participants.

Survey methods

In the KiGGS study, a total of 17,641 children and adolescents aged 0–17 years were interviewed and medically examined. Of those, 14,386 participants aged 1–17 years provided a blood sample. As we could not test around 15% of the sera samples because they were already used up in the core study (n = 14,302), or could not be successfully tested in the laboratory for reasons like insufficient bead count (n = 84), the overall number of serum samples available for this study were 12,257 (85.2%).

Standardized self-administered questionnaires were used to obtain information on socio-demographic and lifestyle variables. Questionnaires were filled out by the parents of all children (1–17 years) and by the children themselves (> 10 years). Age was categorized into seven groups (1–3, 4–6, 7–9, 10–11, 12–13, 14–15, and 16–17). Region of residence was split into two groups, with 'West Germany' and 'East Germany', considering the former boarders of the German Democratic Republic and the Federal Republic of Germany from 1949 to 1990. Urbanity was categorized as rural (< 5000 residents), small city (5000 to < 20,000 residents), medium-sized city (20,000 to < 100,000 residents) and large city (≥ 100,000 residents). The socioeconomic status was based on a parental socioeconomic status (SES) index, including information about education, occupational status, and income of both parents separately. The highest index score was used for the overall household SES. Based on the household SES index, children were categorized into 'low', 'medium' and 'high' SES [38].

Multiplex serology

In 2016/2017, serum specimens were tested for antibodies to the major capsid (L1) protein of 16 different HPV genotypes at the German Cancer Research Center (DKFZ) in Heidelberg. Serological testing was performed by a glutathione *S*-transferase (GST) capture immunoassay in combination with fluorescent bead technology as previously described [39]. We used the following criteria to select HPV-types for analysis: public health relevance, carcinogenic potential, and associated disease outcomes (Additional file 1: Fig. S1). As little is known about different cutaneous HPV types in children apart from the common cutaneous disease types HPV-1 and HPV-4, we tried to include a broad coverage of phylogenetic genera and species for cutHPV. Finally, nine mucosal (alpha: 6, 11, 16, 18, 31, 33, 45, 52, 58) and seven cutaneous (alpha: 10; beta: 8, 38, 49; gamma: 4; nu: 41; mu: 1) HPV genotypes were included in the test panel. We measured type-specific HPV seroreactivity in median fluorescence intensity (MFI) units.

For calculating seropositivity, MFI values were dichotomized as positive or negative based on previously established type-specific cutoff-values. Seropositivity was defined as the proportion (%) of positive tested sera. The cut-off values were established with sera of a cohort of 125 young Korean women who were HPV DNA negative and self-reported to never have had sexual intercourse [40]. The following MFI cutoffs were used for mucHPV: HPV-6: 571, HPV-11: 500, HPV-16: 200, HPV-18: 200, HPV-31: 712, HPV-33: 515, HPV-45: 368, HPV-52: 371, HPV-58: 200. A cutoff of 200 MFI was used for all cutHPV [41].

Statistical analysis

To assure representativeness of the data at the national level, survey weights were calculated and applied to all estimates, adopting the study sample (providing HPV antibody test results) to the population structure of Germany in 2003 in terms of age, gender, state, size of municipality, education and German/non-German nationality and the regional distribution between East and West Germany. These survey weights, which accounted for the stratified and clustered sample design of the survey, were applied throughout the statistical analyses.

Weighted seroprevalence was calculated for all 16 types separately and for the following groups of HPV types: types included in the bivalent vaccine (HPV-2val, 16, 18), types included in the quadrivalent vaccine (HPV-4val, 6, 11, 16, 18), and types included in the nonavalent vaccine (HPV-9val, 6, 11, 16, 18, 31, 33, 45, 52, 58). Group-specific seroprevalence was calculated as the weighted proportion of participants seropositive to at least one of the HPV-types included in one group. Additionally, MFI were plotted against the percentile for each HPV type individually stratified by gender and age for analyzing antibody reactions without relying on a specific cutoff.

Differences regarding demographic and behavioral characteristic of participants stratified by gender were evaluated by using chi^2 or Fishers Exact test. Chi^2-tests were used to test for statistical significance in categorical variables ($p < 0.05$) and logit transformation was applied to calculate confidence intervals (95% CI).

We calculated prevalence ratios (PRs) using Poisson regression models to identify factors independently associated with HPV seropositivity for HPV-6, HPV-11, HPV-16, HPV-18 and for at least one of the cutaneous HPV types (HPV-1, HPV-4, HPV-8, HPV-10, HPV-38, HPV-41, or HPV-49) tested for in our analysis (HPV-cut). We used PR instead of Odds Ratios to obtain more interpretable association estimates [42]. The modelling was performed using generalized linear models with

Poisson family with log link function. Additionally, we included the survey design for estimating variance and 95% CIs. Possible interactions between factors were taken into consideration in the multivariable model. In the final multivariable model, we included all factors that were associated with type-specific seropositivity at a $p < 0.05$ level in a backward step approach. Pearson's correlation coefficient was calculated to identify correlations between HPV types, with attributing small correlation for values between 0.1 and 0.3, moderate correlation for values between 0.3 and 0.5 for strong correlation for values 0.5.

Data management and statistical analysis were conducted using Stata, Version 14 (STATA Corp., College Station, TX, US). Percentile plots were created with R Studio, Version R version 3.6.0 (2019-04-26).

Results

Overall, 12,257 serum samples of children and adolescents aged 1–17 years with valid HPV serology from the pre-HPV-vaccination era were included in the analysis (Fig. 1). Among the participants, 48.7% were girls (n = 5973) and 51.3% were boys (n = 6284). The sociodemographic characteristics of the study population are shown in Table 1.

Seroprevalence mucosal HPV types

Seroprevalence data and MFI distributions of mucHPV are presented in Fig. 2, and Additional file 2: Fig. S2, Additional file 5: Table S1. Seroprevalence of all but HPV-6 ranged from 0.6% (95% CI 0.4–0.8%) for HPV-33, to 6.4% (95% CI 5.8–7.1%) for HPV-31. Type-specific HPV seroprevalence did not differ by gender for most mucHPV, except of HPV-6.

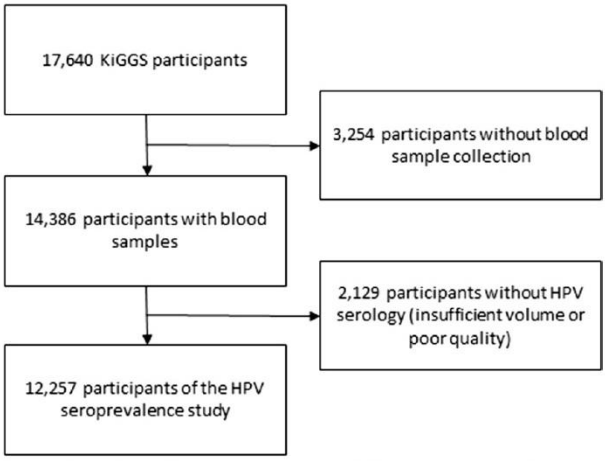

Fig. 1 Flow chart of study participants of the HPV seroprevalence study (n = 12,257, sera collected 2003–2006)

HPV-6 differed to the other mucHPV with a high overall seroprevalence of 24.8% (95% CI 23.6–26.1%). The highest value (33.8%, 95% CI 31.0–36.7%) was observed in the age group 4–6 years. HPV-6 seroprevalence decreased thereafter to 16.6% (95% CI 14.5–19.1%) in the age group 16–17 years. HPV-6 was the only mucHPV which differed by gender with an overall seroprevalence of 23.1% (95% CI 21.5–24.7%) in girls and 26.4% (95% CI 24.9–28.0%) in boys ($p < 0.001$). HPV-11 resembled HPV-6 regarding age distribution with highest seroprevalence in the age group 4–6 years.

The overall seroprevalence of **HPV-16** was 2.6% (95% CI 2.2–3.0%). It remained relatively stable in the youngest age groups with 1.5% (95% CI 0.9–2.6%) among the 1–3 years-old and 2.1% (95% CI 1.4–3.1%) among the 12–13 years-old and increased thereafter to 3.1% (95% CI 2.2–4.2%) and 4.4% (95% CI 3.4–5.8%) among the age groups 14–15 and 16–17 years, respectively.

HPV-18 seroprevalence had a low variability across age groups, with highest seroprevalence in the oldest group (5.1%, 95% CI 4.0–6.4%). Overall, lowest seroprevalence was found for HPV types 33, 45, 52, and 58, with slightly higher values in older age groups. HPV-31 showed the highest seroprevalence (15.1%, 95% CI 12.6–17.9%) in the youngest age group, strongly decreasing at higher age.

Seroprevalence of vaccine relevant HPV types

Overall, 6.1% (95% CI 5.5–6.8%) of the participants were seropositive for at least one of HPV-16 or HPV-18, both types targeted by the bivalent vaccine (HPV-2val) (data not shown). 28.9% (95% CI 27.5–30.4%) were seropositive for at least one of the types covered by the quadrivalent vaccine (HPV-4 val) and around a third (34.0%, 95% CI 32.5–35.6%) were seropositive for one of the nonavalent vaccine types (HPV-9val).

Seroprevalence of cutaneous HPV types

Seroprevalence data and MFI distributions of cutHPV are presented in Fig. 3, Additional file 3: Fig. S3 and Additional file 6: Table S2. CutHPV seroprevalence ranged from 4.0% (95% CI 3.5–4.6%) in girls and 4.0% (95% CI 3.5–4.5%) in boys for HPV-38 to 33.8% (95% CI 32.2–35.5%) in girls and 29.7% (95% CI 28.4–31.1%) in boys for HPV-1 (Additional file 6: Table S2). In most cutHPV, HPV seroprevalence did not differ between boys and girls, except of HPV-1 with 33.8% (95% CI 32.2–35.5%; girls) and 29.7% (95% CI 28.4–31.1% boys) ($p < 0.001$).

CutHPV seroprevalence increased nearly steadily from youngest to oldest age groups. We found the strongest increase in HPV-1 seroprevalence, ranging from 2.1% (95% CI 1.1–4.0%) in 1–3-years-old to 55.7% (95% CI 51.7–59.6%) in 16–17-years-old among girls

Table 1 Demographic characteristics of the study participants stratified by gender, HPV seroprevalence study (n = 12,257, sera collected 2003–2006)

	Females		Males		Total		p-value
	Subjects, no.	%[a]	Subjects, no.	%[a]	Subjects, no.	%[a]	
Overall	5973	48.7	6284	51.3	12,257	100	
Age group (y)							0.248
1–3	616	15.4	649	15.4	1265	15.4	
4–6	882	16.7	933	16.6	1815	16.6	
7–9	1071	17.0	1146	17.0	2217	17.0	
10–11	823	11.4	851	11.4	1674	11.4	
12–13	889	12.2	960	12.2	1849	12.2	
14–15	858	13.6	963	13.6	1821	13.6	
16–17	834	13.8	782	13.8	1616	13.8	
Region of residence							0.426
West Germany	3922	83.2	4169	83.2	8091	83.2	
East Germany	2051	16.8	2115	16.8	4166	16.8	
Urbanity							0.090
Rural	1338	18.3	1382	18.5	2720	18.4	
Small city	1561	27.5	1660	27.4	3221	27.5	
Medium sized city	1768	29.6	1764	29.1	3532	29.3	
Large city	1306	24.6	1478	25.0	2784	24.8	
Socioeconomic status of parents							0.612
Low	1569	33.8	1656	34.3	3225	34.1	
Middle	2744	43.0	2882	42.0	5626	42.5	
High	1523	20.9	1579	21.1	3102	21.0	
NA	137	2.4	167	2.6	304	2.5	
Migratory background of parents							0.319
None	4680	74.2	4891	74.0	9571	74.1	
One parent	403	8.1	431	8.4	834	8.3	
Both parents	861	17.3	943	17.3	1804	17.3	
NA	29	0.5	19	0.3	48	0.4	

NA not available

[a] Weighted proportion

[#] p-value for difference by gender

and from 0.9% (95% CI 0.4–1.8%) in 1–3-years-old to 47.7% (95% CI 43.4–52.0%) in 16–17-years-old among boys.

Taken all seven tested cutaneous HPV types together, 46.0% (95% CI 44.7–47.3%) of the participants were seropositive for at least one HPV-cut type (data not shown). Seroprevalence for HPV-cut increased sharply from 16.0% (95% CI 13.5–18.9%) in the age group 1–3 years to 57.5% (95% CI 54.4–60.6%) among children aged 10–11 years. Thereafter, seroprevalence for HPV-cut remained relatively stable and increased only slightly to 66.9% (95% CI 64.2–69.5%) in age group 16–17. No seroprevalence difference was observed between females and males in overall HPV-cut (p = 0.087).

Seroprevalence of single or multiple HPV types

36.6% (95% CI 35.1–38.2%) of the study population was seronegative for all 16 investigated HPV types. Around a third (32.7%, 95% CI 31.5–34.0%) were seropositive for one HPV type, and 16.8% (95% CI 15.8–17.7%) were seropositive for two HPV types. 7.4% (95% CI 6.7–8.2%) of the study population were seropositive for three HPV types, and 6.5% (95% CI 5.9–7.1%) were seropositive for more than three HPV types. In general, multiple HPV seropositivity was influenced by the high proportion of HPV-6 seropositivity. No gender difference was observed for multiple HPV seropositivity (p = 0.475).

The percentage of children being seronegative to any HPV types decreased from 57.2% (95% CI 53.1–61.1%) among 1–3-years-old to 28.8% (95% CI 26.1–31.6%) among 10–11-years-old children and decreased only

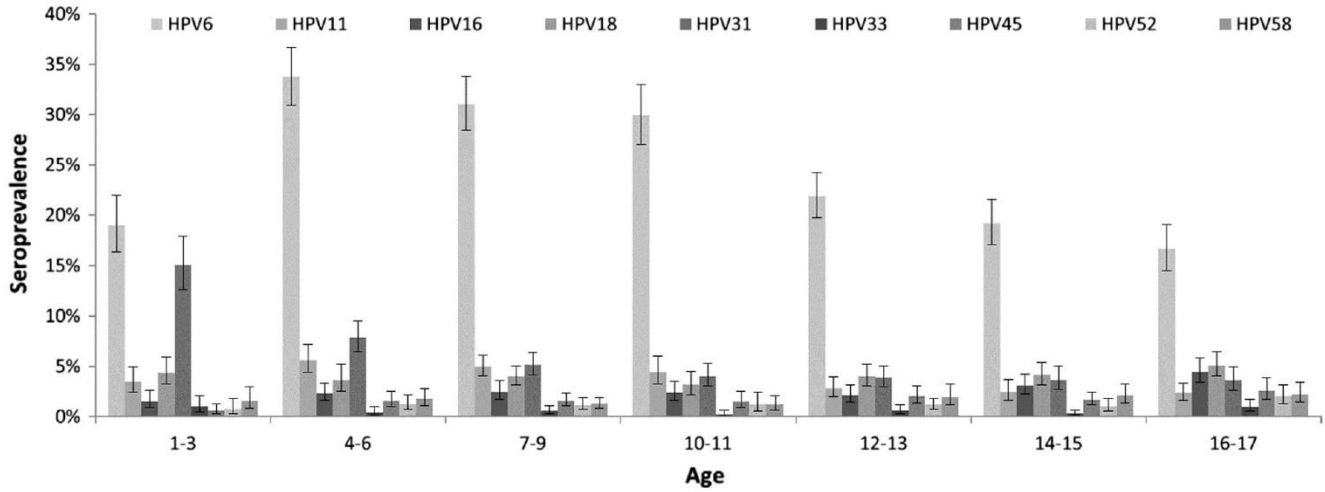

Fig. 2 Seroprevalence of mucosal human papillomavirus types by age, HPV seroprevalence study (n = 12,257, sera collected 2003–2006)

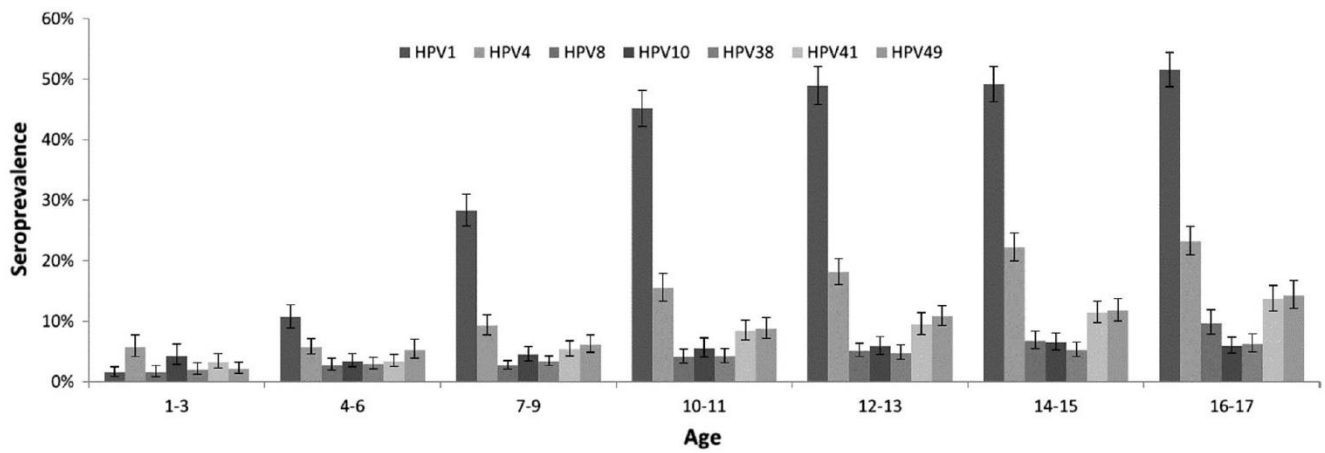

Fig. 3 Seroprevalence of seven cutaneous human papillomavirus types by age, HPV seroprevalence study (n = 12,257, sera collected 2003–2006)

slightly thereafter to 25.7% (95% CI 23.3–28.3%) among the oldest age group (16–17 years) (Additional file 4: Fig. S4). Accordingly, seropositivity for three or more HPV types increased from 4.7% (95% CI 3.6–6.2%) with 3 types and 1.6% (95% CI 0.9–2.8%) with > 3 types among the youngest to 9.6% (95% CI 8.1–11.3%) with 3 types and 12.4% (95% CI 10.3–14.7%) with > 3 types among the oldest age group.

Strong correlation of MFI values was observed among HPV α10 genotypes 6 and 11 (r = 0.85) and HPV α9 types 52 and 58 (r = 0.75). Moderate correlation was observed among α7 types 18 and 45 (r = 0.46) and among α9 types, with HPV types 31/33 (r = 0.39), 33/52 (r = 0.49), and 33/58 (r = 0.49).

Regarding cutHPV, moderate correlation was found only between HPV types 8 and 38 (r = 0.44), 8 and 49 (r = 0.47), and 38 and 49 (r = 0.43).

Factors associated with type-specific seropositivity

We analyzed possible associations of demographic variables with type-specific seropositivity. The weighted crude and adjusted PR for HPV-16 and HPV-cut can be found in Tables 2 and 3, respectively. Results of the regression analysis for HPV-6, HPV-11, and HPV-18 seropositivity are presented in Additional file 7: Table S3, Additional file 8: Table S4 and Additional file 9: Table S5.

In the fully adjusted **HPV-16 model**, only age and region of residence were significantly associated with seropositivity. Children of older age (PR 14–15 years: 2.1, 95% CI 1.2–3.7; 16–17 years: 3.0, 95% CI 1.6–5.6) and children living in West Germany (PR: 0.7, 95% CI 0.5–1.0) were more likely to be seropositive compared to younger age groups and to those living in the eastern part of Germany.

While several associations, like number of household members, or number of sunburns, were significant in

Table 2 Factors associated with seropositivity for HPV-16, HPV seroprevalence study (n = 12,257, sera collected 2003–2006) (results from regression analysis)

	Crude PR (95% CI)	p-value	Fully adjusted PR (95% CI)[a]	p-value
Gender			ns[b]	
Female	Ref			
Male	1.1 (0.8–1.4)	0.706		
Age group (years)				
1–3	Ref		Ref	
4–6	1.5 (0.8–3.0)	0.196	1.5 (0.8–3.0)	0.198
7–9	1.6 (0.8–3.3)	0.158	1.6 (0.8–3.2)	0.167
10–11	1.6 (0.8–3.2)	0.184	1.6 (0.8–3.1)	0.195
12–13	1.4 (0.7–2.8)	0.331	1.4 (0.7–2.8)	0.348
14–15	2.0 (1.1–3.7)	0.018	2.1 (1.2–3.7)	0.015
16–17	3.0 (1.6–5.5)	0.001	3.0 (1.6–5.6)	0.001
Region of residence				
West Germany	Ref		Ref	
East Germany	0.7 (0.5–1.0)	0.055	0.7 (0.5–1.0)	0.025
Urbanity			ns[b]	
Rural	Ref			
Small city	0.8 (0.6–1.3)	0.423		
Medium sized city	0.9 (0.6–1.3)	0.499		
Large city	0.8 (0.5–1.3)	0.370		
Socioeconomic status of parents			ns[b]	
Low	Ref			
Middle	0.8 (0.6–1.1)	0.132		
High	0.8 (0.5–1.1)	0.134		
Migratory background of parents			ns[b]	
None	Ref			
One parent	0.9 (0.5–1.5)	0.596		
Both parents	1.3 (1.0–1.9)	0.077		
Number of household members	1.0 (0.9–1.1)	0.752	ns[b]	
Number of siblings in household	0.9 (0.8–1.1)	0.225		
Body Mass Index (BMI)	1.0 (1.0–1.1)	< 0.001	ns[b]	

PR prevalence ratio, *CI* confidence interval, *Ref* reference

[a] Mutually adjusted for all other variables in the model

[b] ns = variables were not significantly associated with HPV seroprevalence in the final model and therefore excluded

the univariable **HPV-cut model**, a significant association with HPV-cut seropositivity was only observed for age, region of residence, urbanity, and migratory background of parents in the multivariable model. The strongest association with HPV seropositivity for cutHPV was seen for age, with a PR increase from 1.6 (95% CI 1.3–1.9) among the youngest age groups to 4.2 (95% CI 3.5–5.0) among the oldest. Living in East Germany, compared to West Germany, was associated with a slightly lower seropositivity (0.9, 95% CI 0.9–1.0). The same was true for living in medium (0.9, 95% CI 0.9–1.0) or large cities (0.9, 95% CI 0.9–1.0), compared to living in rural areas, as well as for migratory background of parents (0.9, 95% CI 0.8–0.9), compared to non-migratory background.

Region of residence was the only variable which was significantly associated with HPV seropositivity in all five regression models. Children living in West Germany were more likely to be seropositive for HPV-6, HPV-11, HPV-16, HPV-18, and HPV-cut, compared to children living in East Germany. HPV-6 and HPV-11 were the only serotypes for which number of siblings (HPV-6: 1.1, 95% CI 1.1–1.1) or number of household members (HPV-11: 1.1, 95% CI 1.0–1.2) were significantly associated with a slightly higher seropositivity (Additional file 7: Table S3, Additional file 8: Table S4).

Table 3 Factors associated with seropositivity for HPV-cut, HPV seroprevalence study (n = 12,257, sera collected 2003–2006) (results from regression analysis)

	Crude PR (95% CI)	p-value	Fully adjusted PR (95% CI)[a]	p-value
Gender			ns[b]	
Female	Ref			
Male	1.0 (0.9–1.0)	0.086		
Age group (y)				
1–3	Ref		Ref	
4–6	1.6 (1.3–1.9)	< 0.001	1.6 (1.3–1.9)	< 0.001
7–9	2.6 (2.2–3.1)	< 0.001	2.6 (2.2–3.1)	< 0.001
10–11	3.6 (3.0–4.3)	< 0.001	3.6 (3.0–4.3)	< 0.001
12–13	4.0 (3.3–4.7)	< 0.001	3.9 (3.3–4.7)	< 0.001
14–15	4.0 (3.4–4.7)	< 0.001	4.0 (3.4–4.7)	< 0.001
16–17	4.2 (3.5–5.0)	< 0.001	4.2 (3.5–5.0)	< 0.001
Region of residence				
West	Ref		Ref	
East	1.0 (0.9–1.0)	0.084	0.9 (0.9–1.0)	< 0.001
Urbanity				
Rural	Ref		Ref	
Small city	1.0 (0.9–1.0)	0.433	1.0 (0.9–1.0)	0.447
Medium sized city	0.9 (0.8–1.0)	0.006	0.9 (0.9–1.0)	0.042
Large city	0.9 (0.8–0.9)	0.001	0.9 (0.9–1.0)	0.045
Socioeconomic status of parents			ns[b]	
Low	Ref			
Middle	1.0 (1.0–1.1)	0.211		
High	1.0 (0.9–1.0)	0.329		
Migratory background of parents				
None	Ref		Ref	
One parent	0.9 (0.8–1.0)	0.018	1.0 (0.9–1.1)	0.896
Both parents	0.9 (0.8–0.9)	< 0.001	0.9 (0.8–0.9)	0.001
Number of household members	1.0 (1.0–1.1)	0.003	ns[b]	
Number of siblings in household	1.0 (1.0–1.1)	< 0.001	ns[b]	
BMI	1.1 (1.0–1.1)	< 0.001	ns[b]	
Breastfeeding			ns[b]	
Never	Ref			
Yes (but not solely)	1.0 (1.0–1.1)	0.345		
Yes, full till 4th month	0.9 (0.9–1.0)	0.033		
Yes, full till 6th month	0.8 (0.8–0.9)	< 0.001		
Sunburn			ns[b]	
No	Ref			
Yes, several times	1.4 (1.2–1.5)	< 0.001		
Yes, one time	1.4 (1.3–1.4)	< 0.001		
Don't know	1.3 (1.2–1.5)	< 0.001		

PR prevalence ratio, *CI* confidence interval, *Ref* reference

[a] Mutually adjusted for all other variables in the model

[b] ns = variables were not significantly associated with HPV seroprevalence in the final model and therefore excluded

Discussion

Data on HPV infections from the pre-vaccination era are crucial to evaluate the impact of HPV vaccination. Although not all HPV infections lead to seroconversion, population-based seroprevalence studies are suitable to inform about prior cumulative exposure to HPV in different age groups. While most of the serological studies focus on adult population or adolescents, data on

type-specific antibody reactivity in children and adolescents of all ages and both genders are scarce. We examined nationally representative data on children and adolescents aged 1–17 years to determine seroprevalence of nine mucosal and seven cutaneous HPV serotypes in 2003 to 2006, before the introduction of HPV vaccines in Germany.

HPV seroprevalence of mucHPV was generally low among children and adolescents. Type-specific seroprevalence was <3% for HPV-16, 33, 45, 52, and 58, around 4% for HPV-18 and 11, and around 6% for HPV-31. HPV-6 showed relatively high antibody reactivity with around a quarter of the children and adolescents being seropositive. We observed considerable seroprevalences of several mucHPV in children who were above the age of having maternal antibodies gained through a potential vertical transmission and under the age of being sexually active and having gained HPV antibodies through sexual contact. However, most of the children showed low type-specific mucosal antibody titers, compared to cutHPV. Seroprevalence of cutHPV were generally higher, with most HPV types ranging between 4 and 8%, as well as 14% and 32% for HPV-4 and HPV-1, respectively. High reactivity in cutHPV was especially evident for HPV-1, which was present in around 50% of the children above the age of 10 years.

While many international studies have investigated HPV serology in adults, only few serological studies targeted children and adolescents [33, 43–50]. However, most of them are limited by small sample size [41, 49, 51, 52], focus on single or highly selected mucHPV [32, 44, 47], or target specific age groups [50, 53]. Most serological studies do not analyze age-specific seroprevalence of children under the age of 10 (mainly because of small sample size) [41, 43, 45, 51, 52, 54–56], or include only females [45, 57, 58].

The focus on HPV prevalence among infants or adolescents is usually based on different theories and approaches of HPV transmission in children and adolescents. Mainly older studies focused on exploring seroprevalence based on vertical (mainly perinatal) transmission, reporting varying risk of transmission between 4 and 22%. Maternal transmission was addressed by several research papers [16, 20, 21, 27, 59], showing that about 30% of HPV positive children share at least one (cutaneous) HPV type with their mother (or also father) [3]. Although perinatally acquired HPV infections may persist up to 3 years [24, 60, 61], it was concluded that the overall risk of vertical HPV transmission is relatively low [62].

Others have analyzed the age-dependent increase of mucosal HPV seroprevalence in older children and adolescents which was assumed to reflect sexual transmission of HPV due to onset of sexual activity. However, mucosal HPV prevalence was also detected in children of other age groups, irrespective of sexual transmission [16, 18]. Subsequently, it has been increasingly described that mucosal antibody reactions (or HPV DNA detection) in children should not be automatically seen as a reliable marker of sexual abuse and alternative transmission routes of HPV should be considered [3, 20, 27, 56, 63, 64]. Non-sexual and non-vertical HPV infections in children have been described as potentially horizontally transmitted [20], by self- or heteroinoculation (e.g. anogenital to hands or finger to mouth) [3, 16, 65]. This is supported by Syrjanen [63], who describes that typical anogenital HPV types, like HPV 6, 11, or 16, are also commonly found in oral mucosa [66, 67]. The horizontal transmissions may explain the seroprevalence of mucHPV among children in our study. Another explanation is that early acquired infections through vertical transmissions can lead to latent infections in children, which may remain for several years [63, 68].

Type-specific HPV seroprevalence in children showed a considerable variability in previous studies. HPV-16 seroprevalence ranged from 0.0% in a study with 128 children aged 0–9 years in Australia [43] to 10.9% in a study with 46 children aged 2–7 years in South Africa [69]. In a study including 257 male students aged 9–14 years from Mexico City, HPV 16 seroprevalence was 6.2% [70]. A study from Germany including 187 children aged 1–14 years measured a seroprevalence of 0.5% [41]. However, age groups within studies differed substantially and numbers of participants (under the age of 18 years) were small in all studies. A study by Dunne et al. [55], including higher numbers of children, reported an HPV-16 seroprevalence of 2.4% among 1,316 children aged 6–11 years in the United States. They found a seroprevalence of 0.4% among 429 children aged 6–7 and 3.3% among children aged 8–11 years. A study by Cubie and colleagues reported an HPV-16 seroprevalence of 7.6% among 1192 schoolgirls aged 11–13 years, which is higher compared the HPV-16 seroprevalence of 2.7% and 2.1% among girls aged 10–11 and 12–13 years found in our study [50]. A study from Sweden including 1031 children aged 0–13 years calculated an HPV-16 seroprevalence of 3.0% [32], which is comparable to the overall HPV-16 seroprevalence of 2.6% in our study population.

In the same study, HPV-16-seroprevalence was highest (5.2%) among infants aged 0–0.5 years and again high with 6.1% and 3.2% among children aged 7–10 (n = 165) and 10–13 years of age (n = 124) [32]. A bimodal age distribution has been discussed before [18] and was also reported for asymptomatic HPV infections of the oral mucosa, with a first peak prior to 1 year of age and a second peak in adolescence [3]. In our data, HPV-16

seroprevalence remained relatively stable between 1.5 and 2.5% among children under the age of 14 years and increased slightly to 4.4% in the oldest age group, following a rather typical age distribution based on an increased exposure due to sexual transmission of HPV-16 as reported by others [45, 56, 57, 71]. However, it is important to notice, that we could not include infants under the age of 1 year.

An age distribution similar to that of HPV-16 seroprevalence was observed for HPV-18, HPV-45, HPV-52 and HPV-58. The opposite was true for HPV-6, HPV-11, and HPV-31: the highest seroprevalence was observed in younger age groups, followed by lowest HPV seroprevalence in the oldest age groups. This is not in line with results from another study, even though a comparison is limited as younger age groups are combined broadly and numbers are low within those age groups in the study from Australia [43]. However, a bimodal age distribution with high numbers of HPV infections (e.g. HPV-6) among the youngest age groups were also found by DNA testing [72]. Compared to most mucHPV, we observed higher seroprevalence of cutHPV, especially for HPV-1, which is in line with other reports [41, 50].

Using HPV-specific antibodies as a measure of previous infections poses several challenges. While it has been shown that mucosal HPV antibodies can serve as an indicator of previous HPV infections [73], varying seroconversion rates [74] and latency time of antibody development limit their value. In females, following natural infections with HPV, antibody responses are only detectable in about 50–70% of cases [74, 75], with the majority of responses being weak. A study by Antonsson et al. [76] showed that there was little difference in HPV antibody stability between men and women. Another limitation of serological HPV studies is the question of antibody stability over time. Whereas antibody titers have been shown to be relatively stable for mucosal types [73], the stability of cutHPV antibodies is less known [76] and studies with reliable data on the HPV antibody stability among children of different age groups are missing.

It has been discussed whether the development of HPV antibodies (and more generally an HPV infection) in early childhood protects from HPV infection or HPV associated diseases in later life [62, 77, 78]. Naturally acquired HPV antibodies provide protection against subsequent cervical HPV infections [79]. However, the effect of naturally acquired infections on immunity seems to be modest and type-specific, as the effect was only observed for HPV-16 infections [78, 79]. Rodriguez et al. [80] showed that type-specific HPV infections may reappear and may lead to precancerous lesions in previously exposed individuals, even though the risk was low. In addition, the magnitude of antibody response seems to influence immunity as shown in natural acquired compared to vaccination acquired antibody responses [62, 79, 81, 82]. The effect of naturally acquired HPV-16 antibodies seems to be also age-dependent and was lower in women >25 years compared to 15- to 25-year-old women [62]. Focusing on seroprevalence in children and the potential influence of age, the question of naturally acquired immunity is even more relevant when investigating the most appropriate age for vaccination.

In Germany, HPV vaccination is recommended for girls by the Standing Committee on Vaccination (STIKO) since 2007 [83]. In 2018, the recommendation of a two doses HPV vaccine schedule (with an interval of at least 5 month) was extended to all boys and girls at ages 9–14 years [84]. HPV vaccination coverage in Germany is still low but coverage data indicates a steady increase of full (two dose) coverage among 15 year old girls from 27.2% in 2011 to 43.3% in 2018 [85]. Regarding HPV vaccination strategies, it is generally recommended that HPV vaccine should be given to children prior to sexual debut. On the basis of study results showing that children are already exposed to HR HPV types in young ages, it has been argued that prophylactic HPV vaccination could be more beneficial, if given at an earlier time point, e.g. at birth or in early childhood [16].

We observed no difference in HPV seropositivity in children regarding most of the demographic factors, like gender, or socioeconomic status. The significant higher prevalence ratio for HPV-16 seropositivity in the age groups 15–17 years is in line with other publications and an expression of the sexual debut and the increase in sexual contacts. Slightly higher seroprevalence was found in West Germany compared to East Germany both for mucHPV 6, 11, 16 and 18, and for HPV-cut. The regional difference mirrors the old state border between the Federal Republic of Germany and the German Democratic Republic (1949 till 1990). Therefore, it is a potential factor of underlying socio-cultural differences between the two regions and described as a potential factor for prevalence differences of infectious diseases before [86].

There are a few conflicting studies about a potential association between obesity, measured mostly as body mass index, and HPV infections [87–89]. In our data, body mass index was negatively associated with HPV-16 seroprevalence in the univariate model of our data but was not significant in the final model. Even though body mass index may potentially play a role as a psychosocial risk factor in HPV exposure based on its influence on sexual activity [90], our data underline that there is no biological plausibility of such an association as this would have been seen in younger ages as well. We did not find any association between number of household members or number of siblings and HPV-16,

HPV-18, or HPV-cut seropositivity, which could pose as an additional potential risk factor for horizontal HPV transmission [20, 28, 59, 91, 92]. A slightly higher seroprevalence with increasing numbers of siblings or household members was only found for low risk HPV types 6 and 11 in the fully adjusted models, which could be an indicator for hetero-inoculation due to horizontal transmission of HPV through genital warts, lesions in the oral cavity or laryngeal lesions among household members/siblings [3].

We observed a pronounced association of cutHPV seroprevalence with age. This result is in line with other studies, showing a strong increase of cutHPV in early years of childhood [13, 93]. There were no gender differences regarding cutaneous types, which was also expected as prevalence of skin warts is also not gender-specific [93, 94]. An association between ultraviolet radiation exposure and cutaneous HPV infection (mainly of the beta genus) was described in other studies as it may play a role in the development of basal cell carcinoma and squamous cell carcinoma of the skin [95–97]. However, we did not observe any statistical association between number of experienced sunburns and seropositivity of any cutHPV in our data.

Due to the wide range of different mucosal and cutaneous HPV types included in the assay, the determination of seroprevalence largely depends on the applied cut-off value. There is a variety of serological HPV antibody detection methods, a lack of a universal applicable reference, and no standard cutoff values for type-specific HPV serology. Therefore, serological HPV studies often use a most likely negative cohort as the negative reference to calculate cutoff values. This, however, assumes negativity in this cohort and is challenging if the 'true' status is unknown. Our data was based on previous used cutoffs, established in a cohort of South Korean young women who claimed to have never had sexual contacts before and used for other studies with the same serological assay before [41, 44]. However, the challenges of HPV serology methods implicates a limitation in the comparison and explanatory power of seroprevalence differences between studies using different methods. Despite this limitation, the huge sample size of our study allows to compare seroprevalence of different age groups among the children, as they were all tested with the same methods.

Another potential limitation is antibody cross-reactivity for phylogenetically closely related HPV types, which could lead to an overestimation of seroprevalence for some types (e.g., HPV-16 and -33). However, there is no substantial cross-reactivity across phylogenetic species (e.g., alpha 7 and alpha 9, i.e., HPV-16 and -18) or genera, so the majority of our results are expected to reflect type-specific results.

Conclusion

To our knowledge, this is the first study on HPV antibody seroprevalence of cutaneous and mucosal HPV types among a large, representative sample of children and adolescents aged 1–17 years living in Germany. As a result of our study, we found varying age distributions in seroprevalence, dependent on type and tropism and we found low but non-zero seroprevalence for most tested mucHPV among children and adolescents. For HPV-16, only age and regional differences were associated factors with seropositivity. Compared to mucHPV, seroprevalence of cutHPV were higher and generally increased with age. Our study results provide population-based HPV seroprevalence data among children and adolescents and are an important data source of prior cumulative exposure to HPV in different age groups. Our data can serve as additional baseline data to understand the nature of HPV infections among children and adolescents and help evaluating the impact of the HPV vaccine introduction.

Abbreviations

CI: Confidence interval; cutHPV: Cutaneous HPV types; DKFZ: German Cancer Research Center; GNHIES98: German National Health Interview and Examination Survey 1998; HPV: Human papillomavirus; HPV-LR: Selection of low risk HPV types tested in our study: 6, 11; HPV-HR: Selection of high risk HPV types tested in our study: 16, 18, 31, 33, 45, 52, 58; HPV-cut: Selection of cutaneous HPV types tested in our study: 1, 4, 8, 10, 38, 41, 49; HPV-2val: HPV types in the bivalent vaccine: 16, 18; HPV-4val: HPV types in the quadrivalent vaccine: 6, 11, 16, 18; HPV-9val: HPV types in the nonavalent vaccine: 6, 11, 16, 18, 31, 33, 45, 52, 58; KiGGS: German Health Survey for Children and Adolescents; mucHPV: Mucoseal HPV types; RKI: Robert Koch-Institute; PR: Prevalence ratios.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-022-07028-8.

Additional file 1: Figure S1. Selection criteria of HPV types.

Additional file 2: Figure S2. Percentile plot of the antibody reaction (MFI values) of muscosal HPV types HPV-6, HPV-11, HPV-16, HPV-18, HPV31, HPV33, HPV45, HPV52, HPV58, HPV seroprevalence study (n = 12,257, sera collected 2003–2006).

Additional file 3: Figure S3. Percentile plot of the antibody reaction (MFI values) of cutaneous HPV types HPV1, HPV4, HPV8, HPV10, HPV38, HPV41, HPV49, HPV seroprevalence study (n = 12,257, sera collected 2003–2006).

Additional file 4: Figure S4. Multiple HPV seropositivity by age, HPV seroprevalence study (n = 12,257, sera collected 2003–2006).

Additional file 5: Table S1. Seroprevalence of individual mucosal human papillomavirus types by gender and age, HPV seroprevalence study (n = 12,257, sera collected 2003–2006).

Additional file 6: Table S2. Seroprevalence of individual cutaneous human papillomavirus types by gender and age, HPV seroprevalence study (n = 12,257, sera collected 2003–2006).

Additional file 7: Table S3. Regression estimates for associated factors with seropositivity for HPV-6, HPV seroprevalence study (n = 12,257, sera collected 2003–2006).

Additional file 8: Table S4. Regression estimates for associated factors with seropositivity for HPV-11, HPV seroprevalence study (n = 12,257, sera collected 2003–2006).

Additional file 9: Table S5. Regression estimates for associated factors with seropositivity for HPV-18, HPV seroprevalence study (n = 12,257, sera collected 2003–2006).

Acknowledgements
We would especially like to thank all study participants and their parents who were and still are part in the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). The authors wish to acknowledge the work of all colleagues at Robert Koch Institute who were involved in the development and implementation of the KiGGS cohort. We would also like to acknowledge the work of the laboratory staff involved in preparation and performing HPV serology at the German Cancer Research Center (DKFZ) in Heidelberg/Germany.

Authors' contributions
AL: analysis and interpretation of data; drafting of the manuscript; statistical analysis; critical revision of the manuscript. MP, TW: study concept and design; laboratory analysis; analysis and interpretation of data; revision of the manuscript. CP-M, TH, OW, MW-P.: study concept and design; analysis and interpretation of data; revision of the manuscript; study concept and design; analysis and interpretation of data. MT, RL, YD: critical revision of the manuscript. All authors read and approved the final manuscript.

Funding
This work was supported by the German Federal Ministry of Health and by in-house funding of the German Cancer Research Center (DKFZ) in Heidelberg/Germany. The funding source had no involvement in the study design and the preparation, review or approval of the manuscript.

Availability of data and materials
Data cannot be shared publicly because of confidentiality and personal data security restrictions. All data from the "German Health Interview and Examination Survey for Children and Adolescents (KiGGS)" are stored at the national public health institute Robert Koch-Institute. However, data are available upon request from the institutional data access for the scientific community as public use files: https://www.rki.de/EN/Content/Health_Monitoring/HealthSurveys/HealthSurveys_node.

Declarations

Ethics approval and consent to participate
The "German Health Interview and Examination Survey for Children and Adolescents (KiGGS)" was approved by the Charité University Medicine Berlin ethics committee and the Federal Commissioner for Data Protection. Informed written consent and agreement were obtained from the parents of all participants.

Consent of publication
Not applicable.

Competing interests
AL, MP, TH, CP-M, MT, RL, YD, OW, MW-P declared that they have no conflict of interest. TW serves on advisory boards for MSD (Merck) Sharp & Dohme.

Author details
[1]Department for Infectious Disease Epidemiology, Immunization Unit, Robert Koch-Institute, Berlin, Germany. [2]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt- Universität zu Berlin, Berlin, Germany. [3]Infections and Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany. [4]Department of Epidemiology and Health Monitoring, Robert Koch-Institute, Berlin, Germany. [5]GP Practice, Berlin, Germany. [6]Institute of Hygiene and Environmental Medicine, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt- Universität zu Berlin, Berlin, Germany.

Received: 8 July 2021 Accepted: 28 December 2021
Published online: 10 January 2022

References

1. Van Doorslaer K, Li Z, Xirasagar S, Maes P, Kaminsky D, Liou D, Sun Q, Kaur R, Huyen Y, McBride AA. The papillomavirus episteme: a major update to the papillomavirus sequence database. Nucleic Acids Res. 2017;45(D1):D499–506.
2. Lee B, Lee SW, Kim DI, Kim JH. HPV prevalence in the foreskins of asymptomatic healthy infants and children: systematic review and meta-analysis. Sci Rep. 2017;7(1):7050.
3. Syrjanen S. Current concepts on human papillomavirus infections in children. APMIS. 2010;118(6–7):494–509.
4. de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H. Classification of papillomaviruses. Virology. 2004;324(1):17–27.
5. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet. 2007;370(9590):890–907.
6. International Agency on Research on Cancer (IARC). Human papillomaviruses. In: IARC monograohs on the evaluation of carcinogenic risks to humans, vol. 100B. Lyon: International Agency on Research on Cancer; 2012. p. 255–313.
7. Franco EL, Villa LL, Sobrinho JP, Prado JM, Rousseau MC, Desy M, Rohan TE. Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. J Infect Dis. 1999;180(5):1415–23.
8. Giuliano AR, Harris R, Sedjo RL, Baldwin S, Roe D, Papenfuss MR, Abrahamsen M, Inserra P, Olvera S, Hatch K. Incidence, prevalence, and clearance of type-specific human papillomavirus infections: the young women's health study. J Infect Dis. 2002;186(4):462–9.
9. Giuliano AR, Lee JH, Fulp W, Villa LL, Lazcano E, Papenfuss MR, Abrahamsen M, Salmeron J, Anic GM, Rollison DE, et al. Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. Lancet. 2011;377(9769):932–40.
10. Antonsson A, Forslund O, Ekberg H, Sterner G, Hansson BG. The ubiquity and impressive genomic diversity of human skin papillomaviruses suggest a commensalic nature of these viruses. J Virol. 2000;74(24):11636–41.
11. Hufbauer M, Akgül B. Molecular mechanisms of human papillomavirus induced skin carcinogenesis. Viruses. 2017;9(7):187.
12. de Koning MN, Quint KD, Bruggink SC, Gussekloo J, Bouwes Bavinck JN, Feltkamp MC, Quint WG, Eekhof JA. High prevalence of cutaneous warts in elementary school children and the ubiquitous presence of wart-associated human papillomavirus on clinically normal skin. Br J Dermatol. 2015;172(1):196–201.
13. Antonsson A, Karanfilovska S, Lindqvist PG, Hansson BG. General acquisition of human papillomavirus infections of skin occurs in early infancy. J Clin Microbiol. 2003;41(6):2509–14.
14. Costa-Silva M, Fernandes I, Rodrigues AG, Lisboa C. Anogenital warts in pediatric population. An Bras Dermatol. 2017;92(5):675–81.
15. Silverberg MJ, Thorsen P, Lindeberg H, Grant LA, Shah KV. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. Obstet Gynecol. 2003;101(4):645–52.
16. Cason J, Mant CA. High-risk mucosal human papillomavirus infections during infancy & childhood. J Clin Virol. 2005;32(Suppl 1):S52-58.
17. Hajek EF. Contribution to the etiology of laryngeal papilloma in children. J Laryngol Otol. 1956;70(3):166–8.
18. Mammas IN, Sourvinos G, Spandidos DA. The paediatric story of human papillomavirus (Review). Oncol Lett. 2014;8(2):502–6.
19. Pfister H, zur Hausen H. Seroepidemiological studies of human papilloma virus (HPV-1) infections. Int J Cancer. 1978;21(2):161–5.
20. Castellsague X, Drudis T, Canadas MP, Gonce A, Ros R, Perez JM, Quintana MJ, Munoz J, Albero G, de Sanjose S, et al. Human papillomavirus (HPV) infection in pregnant women and mother-to-child transmission of genital HPV genotypes: a prospective study in Spain. BMC Infect Dis. 2009;9:74.
21. Trottier H, Mayrand MH, Coutlee F, Monnier P, Laporte L, Niyibizi J, Carceller AM, Fraser WD, Brassard P, Lacroix J, et al. Human papillomavirus (HPV) perinatal transmission and risk of HPV persistence among children: design, methods and preliminary results of the HERITAGE study. Papillomavirus Res. 2016;2:145–52.

22. Lee SM, Park JS, Norwitz ER, Koo JN, Oh IH, Park JW, Kim SM, Kim YH, Park C-W, Song YS. Risk of vertical transmission of human papillomavirus throughout pregnancy: a prospective study. PLoS ONE. 2013;8(6):e66368–e66368.
23. Rintala MA, Grenman SE, Puranen MH, Isolauri E, Ekblad U, Kero PO, Syrjanen SM. Transmission of high-risk human papillomavirus (HPV) between parents and infant: a prospective study of HPV in families in Finland. J Clin Microbiol. 2005;43(1):376–81.
24. Cason J, Kaye JN, Jewers RJ, Kambo PK, Bible JM, Kell B, Shergill B, Pakarian F, Raju KS, Best JM. Perinatal infection and persistence of human papillomavirus types 16 and 18 in infants. J Med Virol. 1995;47(3):209–18.
25. Doerfler D, Bernhaus A, Kottmel A, Sam C, Koelle D, Joura EA. Human papilloma virus infection prior to coitarche. Am J Obstet Gynecol. 2009;200(5):487.e481.
26. Sabeena S, Bhat P, Kamath V, Arunkumar G. Possible non-sexual modes of transmission of human papilloma virus. J Obstet Gynaecol Res. 2017;43(3):429–35.
27. Sinclair KA, Woods CR, Kirse DJ, Sinal SH. Anogenital and respiratory tract human papillomavirus infections among children: age, gender, and potential transmission through sexual abuse. Pediatrics. 2005;116(4):815–25.
28. Liu Z, Rashid T, Nyitray AG. Penises not required: a systematic review of the potential for human papillomavirus horizontal transmission that is non-sexual or does not include penile penetration. Sex Health. 2016;13(1):10–21.
29. Abreu AL, Souza RP, Gimenes F, Consolaro ME. A review of methods for detect human papillomavirus infection. Virol J. 2012;9:262.
30. Robbins HA, Li Y, Porras C, Pawlita M, Ghosh A, Rodriguez AC, Schiffman M, Wacholder S, Kemp TJ, Gonzalez P, et al. Glutathione *S*-transferase L1 multiplex serology as a measure of cumulative infection with human papillomavirus. BMC Infect Dis. 2014;14:120.
31. Tiggelaar SM, Lin MJ, Viscidi RP, Ji J, Smith JS. Age-specific human papillomavirus antibody and deoxyribonucleic acid prevalence: a global review. J Adolesc Health. 2012;50(2):110–31.
32. af Geijersstam V, Eklund C, Wang Z, Sapp M, Schiller JT, Dillner J, Dillner L. A survey of seroprevalence of human papillomavirus types 16, 18 and 33 among children. Int J Cancer. 1999;80(4):489–93.
33. Scherpenisse M, Mollers M, Schepp RM, Boot HJ, Meijer CJ, Berbers GA, van der Klis FR, de Melker HE. Changes in antibody seroprevalence of seven high-risk HPV types between nationwide surveillance studies from 1995–96 and 2006–07 in The Netherlands. PLoS ONE. 2012;7(11): e48807.
34. Marais D, Rose RC, Williamson AL. Age distribution of antibodies to human papillomavirus in children, women with cervical intraepithelial neoplasia and blood donors from South Africa. J Med Virol. 1997;51(2):126–31.
35. Kurth BM, Bergmann KE, Holling H, Kahl H, Kamtsiuris P, Thefeld W. The national child and adolescent health survey. The complete concept. Gesundheitswesen (Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany)). 2002;64(Suppl 1):S3–11.
36. Kamtsiuris P, Lange M, Schaffrath Rosario A. The German health interview and examination survey for children and adolescents (KiGGS): sample design, response and nonresponse analysis. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2007;50(5–6):547–56.
37. Kurth BM, Kamtsiuris P, Holling H, Schlaud M, Dolle R, Ellert U, Kahl H, Knopf H, Lange M, Mensink GB, et al. The challenge of comprehensively mapping children's health in a nation-wide health survey: design of the German KiGGS-study. BMC Public Health. 2008;8:196.
38. Lange M, Kamtsiuris P, Lange C, Schaffrath Rosario A, Stolzenberg H, Lampert T. Sociodemographic characteristics in the German health interview and examination survey for children and adolescents (KiGGS)—operationalisation and public health significance, taking as an example the assessment of general state of health. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2007;50(5–6):578–89.
39. Waterboer T, Sehr P, Michael KM, Franceschi S, Nieland JD, Joos TO, Templin MF, Pawlita M. Multiplex human papillomavirus serology based on in situ-purified glutathione *s*-transferase fusion proteins. Clin Chem. 2005;51(10):1845–53.
40. Clifford GM, Shin HR, Oh JK, Waterboer T, Ju YH, Vaccarella S, Quint W, Pawlita M, Franceschi S. Serologic response to oncogenic human papillomavirus types in male and female university students in Busan, South Korea. Cancer Epidemiol Biomark Prevent. 2007;16(9):1874–9.
41. Michael KM, Waterboer T, Sehr P, Rother A, Reidel U, Boeing H, Bravo IG, Schlehofer J, Gartner BC, Pawlita M. Seroprevalence of 34 human papillomavirus types in the German general population. PLoS Pathog. 2008;4(6): e1000091.
42. Espelt A, Mari-Dell'Olmo M, Penelo E, Bosque-Prous M. Applied prevalence ratio estimation with different regression models: an example from a cross-national study on substance use research. Adicciones. 2016;29(2):105–12.
43. Newall AT, Brotherton JM, Quinn HE, McIntyre PB, Backhouse J, Gilbert L, Esser MT, Erick J, Bryan J, Formica N, et al. Population seroprevalence of human papillomavirus types 6, 11, 16, and 18 in men, women, and children in Australia. Clin Infect Dis. 2008;46(11):1647–55.
44. Scherpenisse M, Mollers M, Schepp RM, Boot HJ, de Melker HE, Meijer CJ, Berbers GA, van der Klis FR. Seroprevalence of seven high-risk HPV types in The Netherlands. Vaccine. 2012;30(47):6686–93.
45. Kramer M, Mollema L, Smits G, Boot H, de Melker H, van der Klis F. Age-specific HPV seroprevalence among young females in The Netherlands. Sex Transm Infect. 2010;86(7):494–9.
46. Heiligenberg M, Michael KM, Kramer MA, Pawlita M, Prins M, Coutinho RA, Dukers-Muijrers NH, Waterboer T. Seroprevalence and determinants of eight high-risk human papillomavirus types in homosexual men, heterosexual men, and women: a population-based study in Amsterdam. Sex Transm Dis. 2010;37(11):672–80.
47. Lupi S, Bergamini M, Guidi E, Gregorio P. Cross-sectional seroprevalence of antibodies against 6, 11, 16 and 18 human papilloma virus (HPV) types among teenagers and young women in Italy. Annali dell'Istituto superiore di sanita. 2014;50(2):171–7.
48. Joura EA, Kjaer SK, Wheeler CM, Sigurdsson K, Iversen OE, Hernandez-Avila M, Perez G, Brown DR, Koutsky LA, Tay EH, et al. HPV antibody levels and clinical efficacy following administration of a prophylactic quadrivalent HPV vaccine. Vaccine. 2008;26(52):6844–51.
49. Hamsikova E, Ludvikova V, Stasikova J, Tachezy R. Cross-sectional study on the prevalence of HPV antibodies in the general population of the Czech Republic. Sex Transm Infect. 2013;89(2):133–7.
50. Cubie HA, Plumstead M, Zhang W, de Jesus O, Duncan LA, Stanley MA. Presence of antibodies to human papillomavirus virus-like particles (VLPs) in 11–13-year-old schoolgirls. J Med Virol. 1998;56(3):210–6.
51. Mund K, Han C, Daum R, Helfrich S, Muller M, Fisher SG, Schiller JT, Gissmann L. Detection of human papillomavirus type 16 DNA and of antibodies to human papillomavirus type 16 proteins in children. Intervirology. 1997;40(4):232–7.
52. Hamsikova E, Ludvikova V, Smahel M, Sapp M, Vonka V. Prevalence of antibodies to human papillomaviruses in the general population of the Czech Republic. Int J Cancer. 1998;77(5):689–94.
53. Manns A, Strickler HD, Wikktor SZ, Pate EJ, Gray R, Waters D. Low incidence of human papillomavirus type 16 antibody seroconversion in young children. Pediatr Infect Dis J. 1999;18(9):833–5.
54. Chen CJ, Viscidi RP, Chuang CH, Huang YC, Chiu CH, Lin TY. Seroprevalence of human papillomavirus types 16 and 18 in the general population in Taiwan: implication for optimal age of human papillomavirus vaccination. J Clin Virol. 2007;38(2):126–30.
55. Dunne EF, Karem KL, Sternberg MR, Stone KM, Unger ER, Reeves WC, Markowitz LE. Seroprevalence of human papillomavirus type 16 in children. J Infect Dis. 2005;191(11):1817–9.
56. Vos RA, Pasmans H, Tymchenko L, Janga-Jansen AVA, Baboe-Kalpoe S, Hulshof K, de Melker HE, van der Klis FRM. High seroprevalence of multiple high-risk human papillomavirus types among the general population of Bonaire, St. Eustatius and Saba, Caribbean Netherlands. Vaccine. 2020;38(13):2816–26.
57. Jit M, Vyse A, Borrow R, Pebody R, Soldan K, Miller E. Prevalence of human papillomavirus antibodies in young female subjects in England. Br J Cancer. 2007;97(7):989–91.
58. Lehtinen M, Kaasila M, Pasanen K, Patama T, Palmroth J, Laukkanen P, Pukkala E, Koskela P. Seroprevalence atlas of infections with oncogenic and non-oncogenic human papillomaviruses in Finland in the 1980s and 1990s. Int J Cancer. 2006;119(11):2612–9.
59. Syrjanen S, Puranen M. Human papillomavirus infections in children: the potential role of maternal transmission. Crit Rev Oral Biol Med. 2000;11(2):259–74.

60. Kaye JN, Starkey WG, Kell B, Biswas C, Raju KS, Best JM, Cason J. Human papillomavirus type 16 in infants: use of DNA sequence analyses to determine the source of infection. J Gen Virol. 1996;77(6):1139–43.
61. Rintala MA, Grenman SE, Jarvenkyla ME, Syrjanen KJ, Syrjanen SM. High-risk types of human papillomavirus (HPV) DNA in oral and genital mucosa of infants during their first 3 years of life: experience from the Finnish HPV family study. Clin Infect Dis. 2005;41(12):1728–33.
62. Castellsague X, Naud P, Chow SN, Wheeler CM, Germar MJ, Lehtinen M, Paavonen J, Jaisamrarn U, Garland SM, Salmeron J, et al. Risk of newly detected infections and cervical abnormalities in women seropositive for naturally acquired human papillomavirus type 16/18 antibodies: analysis of the control arm of PATRICIA. J Infect Dis. 2014;210(4):517–34.
63. Syrjänen S. Oral manifestations of human papillomavirus infections. Eur J Oral Sci. 2018;126(Suppl 1):49–66.
64. Rice PS, Cason J, Best JM, Banatvala JE. High risk genital papillomavirus infections are spread vertically. Rev Med Virol. 1999;9(1):15–21.
65. Sonnex C, Strauss S, Gray JJ. Detection of human papillomavirus DNA on the fingers of patients with genital warts. Sex Transm Infect. 1999;75(5):317–9.
66. Rice PS, Mant C, Cason J, Bible JM, Muir P, Kell B, Best JM. High prevalence of human papillomavirus type 16 infection among children. J Med Virol. 2000;61(1):70–5.
67. Marais DJ, Sampson C, Jeftha A, Dhaya D, Passmore JA, Denny L, Rybicki EP, Van Der Walt E, Stephen LX, Williamson AL. More men than women make mucosal IgA antibodies to human papillomavirus type 16 (HPV-16) and HPV-18: a study of oral HPV and oral HPV antibodies in a normal healthy population. BMC Infect Dis. 2006;6:95.
68. Heim K, Hudelist G, Geier A, Szedenik H, Christensen ND, Concin N, Bergant A, Volgger B, Czerwenka K, Hopfl R. Type-specific antiviral antibodies to genital human papillomavirus types in mothers and newborns. Reprod Sci. 2007;14(8):806–14.
69. Marais D, Rose RC, Lane C, Aspinall S, Bos P, Williamson AL. Seroresponses to virus-like particles of human papillomavirus types 16, 18, 31, 33, and 45 in San people of Southern Africa. J Med Virol. 2000;60(3):331–6.
70. Pacheco-Dominguez RL, Durazo-Arvizu RA, Lopez-Hernandez A, Figueroa-Padilla J, Ramirez-Gonzalez JB, Lopez-Cervantes M. Seroprevalence of HPV serotypes 6, 11, 16 and 18 in unvaccinated children from Mexico City. Epidemiol Infect. 2019;147:e257.
71. Ryding J, French KM, Naucler P, Barnabas RV, Garnett GP, Dillner J. Seroepidemiology as basis for design of a human papillomavirus vaccination program. Vaccine. 2008;26(41):5263–8.
72. Syrjänen S, Rintala M, Sarkola M, Willberg J, Rautava J, Koskimaa H, Paaso A, Syrjänen K, Grénman S, Louvanto K. Oral human papillomavirus infection in children during the first 6 years of life, Finland. Emerg Infect Dis J. 2021;27(3):759.
73. Dillner J. The serological response to papillomaviruses. Semin Cancer Biol. 1999;9(6):423–30.
74. Carter JJ, Koutsky LA, Hughes JP, Lee SK, Kuypers J, Kiviat N, Galloway DA. Comparison of human papillomavirus types 16, 18, and 6 capsid antibody responses following incident infection. J Infect Dis. 2000;181(6):1911–9.
75. Stanley M. HPV—immune response to infection and vaccination. Infect Agent Cancer. 2010;5:19.
76. Antonsson A, Green AC, Mallitt KA, O'Rourke PK, Pandeya N, Pawlita M, Waterboer T, Neale RE. Prevalence and stability of antibodies to 37 human papillomavirus types—a population-based longitudinal study. Virology. 2010;407(1):26–32.
77. Franceschi S, Baussano I. Naturally acquired immunity against human papillomavirus (HPV): why it matters in the HPV vaccine era. J Infect Dis. 2014;210(4):507–9.
78. Rosillon D, Baril L, Del Rosario-Raymundo MR, Wheeler CM, Skinner SR, Garland SM, Salmeron J, Lazcano-Ponce E, Vallejos CS, Stoney T, et al. Risk of newly detected infections and cervical abnormalities in adult women seropositive or seronegative for naturally acquired HPV-16/18 antibodies. Cancer Med. 2019;8(10):4938–53.
79. Beachler DC, Jenkins G, Safaeian M, Kreimer AR, Wentzensen N. Natural acquired immunity against subsequent genital human papillomavirus infection: a systematic review and meta-analysis. J Infect Dis. 2016;213(9):1444–54.
80. Rodriguez AC, Schiffman M, Herrero R, Hildesheim A, Bratti C, Sherman ME, Solomon D, Guillen D, Alfaro M, Morales J, et al. Low risk of type-specific carcinogenic HPV re-appearance with subsequent cervical intraepithelial neoplasia grade 2/3. Int J Cancer. 2012;131(8):1874–81.
81. Safaeian M, Porras C, Pan Y, Kreimer A, Schiller JT, Gonzalez P, Lowy DR, Wacholder S, Schiffman M, Rodriguez AC, et al. Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica Vaccine Trial. Cancer Prev Res. 2013;6(11):1242–50.
82. Mesher D, Stanford E, White J, Findlow J, Warrington R, Das S, Pebody R, Borrow R, Soldan K. HPV serology testing confirms high HPV immunisation coverage in England. PLoS ONE. 2016;11(3): e0150107.
83. Ständige Impfkommission (STIKO). Mitteilung der Ständigen Impfkommission (STIKO) am Robert Koch-Institut: Impfung gegen humane Papillomaviren (HPV) für Mädchen von 12 bis 17 Jahren - Empfehlung und Begründung. Epidemiol Bull. 2007;12:97–103.
84. AG HPV der Ständigen Impfkommission (STIKO). Wissenschaftliche Begründung für die Empfehlung der HPV-Impfung für Jungen im Alter von 9 bis 14 Jahren. In: Epidemiol Bull. 2018. p. 233–50.
85. Rieck TFM, Wichmann O, Siedler A. Impfquoten von Kinderschutzimpfungen in Deutschland – aktuelle Ergebnisse aus der RKI-Impfsurveillance. Epidemiol Bull. 2020;32(33):9–27.
86. Lachmann R, Loenenbach A, Waterboer T, Brenner N, Pawlita M, Michel A, Thamm M, Poethko-Muller C, Wichmann O, Wiese-Posselt M. Cytomegalovirus (CMV) seroprevalence in the adult population of Germany. PLoS One. 2018;13(7): e0200267.
87. Nyitray AG, Peng F, Day RS, Carvalho Da Silva RJ, Baggio ML, Salmeron J, Quiterio M, Abrahamsen M, Lazcano-Ponce E, Villa LL, et al. The association between body mass index and anal canal human papillomavirus prevalence and persistence: the HIM study. Hum Vaccines Immunother. 2019;15(7–8):1911–9.
88. Jung US, Choi JS, Ko JH, Lee JH, Park SY, Park SH. Decreased prevalence of high-risk human papillomavirus infection is associated with obesity. Eur J Gynaecol Oncol. 2013;34(1):70–4.
89. Liu S-H, Rositch AF, Viscidi RP, Silver MI, Burke AE, Gravitt PE. Obesity and human papillomavirus infection in perimenopausal women. J Infect Dis. 2013;208(7):1071–80.
90. Kershaw TS, Arnold A, Lewis JB, Magriples U, Ickovics JR. The skinny on sexual risk: the effects of BMI on STI incidence and risk. AIDS Behav. 2011;15(7):1527–38.
91. Weissenborn SJ, De Koning MN, Wieland U, Quint WG, Pfister HJ. Intrafamilial transmission and family-specific spectra of cutaneous betapapillomaviruses. J Virol. 2009;83(2):811–6.
92. Bussen S, Sutterlin M, Schmidt U, Bussen D. Anogenital warts in childhood—always a marker for sexual abuse? Geburtshilfe Frauenheilkd. 2012;72(1):43–8.
93. Tamer E, Ilhan MN, Polat M, Lenk N, Alli N. Prevalence of skin diseases among pediatric patients in Turkey. J Dermatol. 2008;35(7):413–8.
94. Williams HC, Pottier A, Strachan D. The descriptive epidemiology of warts in British schoolchildren. Br J Dermatol. 1993;128(5):504–11.
95. Hampras SS, Giuliano AR, Lin HY, Fisher KJ, Abrahamsen ME, Sirak BA, Iannacone MR, Gheit T, Tommasino M, Rollison DE. Natural history of cutaneous human papillomavirus (HPV) infection in men: the HIM study. PLoS One. 2014;9(9): e104843.
96. Sampogna F, Bavinck JN, Pawlita M, Abeni D, Harwood CA, Proby CM, Feltkamp MC, Euvrard S, Naldi L, Neale RE, et al. Factors associated with the seroprevalence of 26 cutaneous and two genital human papillomavirus types in organ transplant patients. J Gen Virol. 2012;93(Pt 1):165–74.
97. Iannacone MR, Wang W, Stockwell HG, O'Rourke K, Giuliano AR, Sondak VK, Messina JL, Roetzheim RG, Cherpelis BS, Fenske NA, et al. Sunlight exposure and cutaneous human papillomavirus seroreactivity in basal cell and squamous cell carcinomas of the skin. J Infect Dis. 2012;206(3):399–406.

Publisher's Note

Anhang Publikation 3

Table S1. Seroprevalence of Individual Mucosal Human Papillomavirus Types by Gender and Age, HPV Seroprevalence Study (n = 12,257, sera collected 2003-2006).

Group	Subjects, no.	Seroprevalence by HPV type, % (95%CI)								
		6	11	16	18	31	33	45	52	58
Overall	12257	24.8 (23.6-26.1)	3.8 (3.3-4.4)	2.6 (2.2-3.0)	4.1 (3.5-4.7)	6.4 (5.8-7.1)	0.6 (0.4-0.8)	1.6 (1.4-1.9)	1.2 (1.0-1.5)	1.7 (1.4-2.1)
		2944	445	309	465	686	68	202	127	181
Females	5973	23.1 (21.5-24.7)	3.8 (3.2-4.5)	2.5 (2.0-3.1)	3.7 (3.0-4.4)	6.4 (5.5-7.4)	0.7 (0.4-1.0)	1.6 (1.2-2.0)	1.2 (0.9-1.6)	1.7 (1.3-2.3)
Age groups		1302	205	150	222	337	34	105	61	90
1-3	615	18.4 (14.7-22.8)	2.7 (1.6-4.6)	1.5 (0.8-2.8)	4.0 (2.4-6.4)	14.4 (11.0-18.6)	1.1 (0.4-3.0)	0.9 (0.4-2.2)	0.3 (0.1-1.1)	0.9 (0.3-2.4)
		115	17	11	24	85	6	7	3	5
4-6	882	31.6 (27.5-36.0)	6.4 (4.4-9.1)	2.1 (1.2-3.6)	2.6 (1.6-4.0)	7.6 (5.8-9.8)	0.7 (0.3-1.9)	1.2 (0.6-2.6)	0.9 (0.4-2.2)	1.7 (1.0-3.0)
		246	47	16	25	68	6	10	8	17
7-9	1071	28.1 (24.9-31.5)	5.1 (3.7-6.9)	2.2 (1.2-4.2)	3.6 (2.5-5.1)	5.7 (4.1-7.7)	0.2 (0.1-0.6)	1.0 (0.5-2.0)	0.9 (0.4-2.0)	1.2 (0.6-2.3)
		296	50	16	37	60	6	13	10	11
10-11	823	26.2 (22.4-30.5)	4.4 (2.9-6.8)	2.7 (1.7-4.2)	3.7 (2.3-5.9)	5.0 (3.5-7.0)	0.3 (0.1-1.3)	1.8 (0.9-3.6)	1.5 (0.6-3.8)	1.1 (0.5-2.3)
		201	34	22	27	39	2	12	5	7
12-13	889	20.3 (17.1-23.9)	2.5 (1.5-4.2)	2.1 (1.2-3.7)	4.4 (3.1-6.4)	3.4 (2.2-5.2)	0.8 (0.3-1.9)	2.5 (1.4-4.2)	1.2 (0.6-2.3)	2.6 (1.4-4.9)
		167	23	20	35	30	5	20	9	17
14-15	858	17.4 (14.6-20.7)	1.8 (1.0-3.2)	3.7 (2.4-5.6)	3.6 (2.5-5.1)	3.0 (1.8-4.7)	0.0 (0.0-0.0)	1.8 (1.1-2.8)	0.6 (0.2-1.5)	2.0 (0.9-4.3)
		142	16	31	35	23	0	20	5	14
16-17	834	17.1 (14.3-20.3)	2.9 (1.7-4.7)	3.9 (2.7-5.6)	4.1 (2.9-5.9)	4.0 (2.6-6.3)	1.4 (0.7-2.8)	2.4 (1.5-3.7)	3.2 (1.9-5.4)	2.5 (1.4-4.3)
		134	18	34	39	31	9	23	20	18
Males	6284	26.4 (24.9-28.0)	3.8 (3.2-4.5)	2.7 (2.2-3.2)	4.5 (3.7-5.3)	6.4 (5.5-7.5)	0.6 (0.4-0.8)	1.7 (1.3-2.1)	1.2 (0.8-1.7)	1.7 (1.3-2.3)
Age groups		1642	240	159	243	349	34	97	66	91
1-3	649	19.3 (15.7-23.5)	4.2 (2.6-6.8)	1.6 (0.7-3.3)	4.7 (3.0-7.3)	15.5 (12.3-19.3)	0.9 (0.3-2.7)	0.4 (0.1-1.1)	1.0 (0.3-3.3)	2.1 (0.9-4.6)
		141	28	10	27	99	6	4	3	7
4-6	933	35.8 (32.2-39.5)	4.9 (3.5-6.8)	2.6 (1.6-4.0)	4.7 (3.0-7.2)	8.1 (6.1-10.9)	0.2 (0.1-0.8)	1.9 (1.0-3.5)	1.5 (0.7-3.2)	1.8 (0.9-3.4)
		338	49	27	34	66	2	11	11	12
7-9	1146	33.9 (30.4-37.5)	4.9 (3.6-6.6)	2.7 (1.6-4.5)	4.4 (3.2-6.1)	4.6 (3.4-6.3)	0.9 (0.4-1.9)	2.1 (1.2-3.5)	1.3 (0.7-2.7)	1.4 (0.8-2.4)
		382	62	29	44	58	8	20	14	17
10-11	851	33.4 (29.4-37.7)	4.4 (3.0-6.4)	2.1 (1.1-4.0)	2.6 (1.5-4.8)	3.1 (1.9-4.9)	0.1 (0.0-0.6)	1.2 (0.5-2.7)	0.8 (0.4-2.0)	1.3 (0.5-3.1)
		257	34	15	19	28	1	8	7	9
12-13	960	23.4 (20.3-26.8)	3.1 (1.9-5.0)	2.1 (1.3-3.4)	3.6 (2.4-5.3)	4.4 (3.1-6.1)	0.5 (0.2-1.3)	1.7 (0.9-3.2)	1.2 (0.7-2.2)	1.4 (0.7-2.6)
		209	24	22	37	38	4	17	12	14
14-15	963	20.8 (17.9-24.1)	3.1 (1.9-5.1)	2.5 (1.6-3.9)	4.7 (3.2-6.8)	4.4 (2.8-6.6)	0.6 (0.3-1.3)	1.6 (0.9-2.9)	1.4 (0.7-2.9)	2.1 (1.2-3.8)
		196	26	25	44	33	7	19	12	17
16-17	782	16.2 (13.1-19.9)	1.9 (1.1-3.2)	5.0 (3.4-7.3)	6.0 (4.3-8.4)	3.2 (2.1-5.0)	0.6 (0.3-1.4)	2.8 (1.5-5.0)	0.9 (0.4-2.3)	2.0 (1.1-3.7)
		119	17	31	38	27	6	18	7	15

NOTE. CI, confidence interval

Table S2. Seroprevalence of Individual Cutaneous Human Papillomavirus Types by Gender and Age, HPV Seroprevalence Study (n = 12,257, sera collected 2003-2006).

Group	Subjects, no.	Seroprevalence by HPV type, % (95%CI)						
		1	4	8	10	38	41	49
Overall	12257	31.7 (30.6-32.8)	13.6 (12.8-14.4)	4.5 (4.1-5.0)	5.0 (4.5-5.6)	4.0 (3.6-4.4)	7.5 (6.8-8.3)	8.1 (7.3-9.0)
		4181	1757	563	591	504	943	1022
Females	5973	33.8 (32.2-35.5)	13.7 (12.7-14.8)	4.3 (3.7-4.9)	5.3 (4.6-6.1)	4.0 (3.5-4.6)	8.0 (7.1-9.0)	7.9 (6.9-8.9)
Age, years		2162	871	284	291	246	487	499
1-3	615	2.1 (1.1-4.0)	5.4 (3.5-8.4)	1.5 (0.6-3.7)	3.5 (1.9-6.2)	2.0 (1.0-4.0)	2.2 (1.2-3.9)	1.7 (0.9-2.9)
		10	31	6	18	11	15	15
4-6	882	10.6 (8.1-13.7)	6.6 (4.8-9.0)	1.6 (0.9-2.6)	4.1 (2.6-6.6)	2.5 (1.6-3.8)	4.0 (2.7-5.8)	3.6 (2.3-5.6)
		81	61	19	31	23	37	30
7-9	1071	29.3 (25.6-33.2)	11.5 (9.1-14.4)	2.4 (1.6-3.5)	5.9 (4.3-8.1)	3.9 (2.8-5.4)	5.4 (4.0-7.2)	6.0 (4.4-8.2)
		315	114	32	53	41	59	64
10-11	823	50.5 (46.4-54.6)	13.6 (10.7-17.1)	3.0 (2.0-4.5)	4.6 (3.0-6.8)	3.1 (1.9-5.1)	9.4 (7.1-12.4)	7.7 (5.6-10.4)
		396	117	31	35	22	63	64
12-13	889	51.2 (46.6-55.7)	18.5 (15.7-21.7)	4.7 (3.4-6.5)	6.0 (4.0-8.7)	4.1 (2.9-5.8)	10.3 (7.9-13.4)	11.8 (9.7-14.2)
		450	162	46	51	38	89	108
14-15	858	51.9 (48.0-55.9)	21.5 (18.5-24.7)	8.0 (6.0-10.4)	6.4 (4.6-8.8)	6.2 (4.5-8.4)	12.5 (10.2-15.3)	11.7 (9.3-14.6)
		445	188	66	49	50	98	94
16-17	834	55.7 (51.7-59.6)	22.6 (19.8-25.8)	9.9 (7.3-13.3)	6.7 (4.8-9.1)	6.9 (5.3-9.1)	14.8 (12.1-18.1)	15.2 (12.2-18.8)
		465	198	84	54	61	126	124
Males	6284	29.7 (28.4-31.1)	13.5 (12.4-14.6)	4.7 (4.1-5.4)	4.8 (4.1-5.6)	4.0 (3.5-4.5)	7.1 (6.2-8.1)	8.4 (7.3-9.5)
Age, years		2019	886	279	300	258	456	523
1-3	649	0.9 (0.4-1.8)	6.0 (3.9-9.3)	1.5 (0.7-3.1)	5.0 (3.0-8.1)	1.9 (1.0-3.8)	4.3 (2.7-6.9)	2.6 (1.4-4.7)
		9	32	9	24	14	25	17
4-6	933	10.7 (8.4-13.6)	4.9 (3.6-6.8)	3.8 (2.5-5.9)	2.7 (1.8-4.0)	3.4 (2.2-5.2)	2.8 (1.9-4.2)	6.8 (4.7-9.7)
		81	52	28	32	27	32	48
7-9	1146	27.3 (24.4-30.3)	7.2 (5.7-9.0)	3.0 (2.1-4.4)	3.1 (2.1-4.6)	2.9 (2.0-4.0)	5.3 (3.7-7.6)	6.3 (4.7-8.4)
		301	98	35	39	42	57	72
10-11	851	40.0 (35.9-44.2)	17.3 (14.2-20.9)	5.1 (3.5-7.3)	6.4 (4.5-9.0)	5.2 (3.7-7.2)	7.5 (5.7-9.7)	9.7 (7.5-12.5)
		346	128	39	44	41	71	86
12-13	960	46.8 (42.5-51.2)	17.7 (14.7-21.2)	5.5 (4.1-7.4)	5.7 (4.0-8.1)	5.3 (3.7-7.7)	8.6 (6.6-11.2)	9.9 (7.6-12.7)
		451	160	50	52	43	79	95
14-15	963	46.6 (42.5-50.7)	22.8 (19.8-26.1)	5.6 (4.1-7.6)	6.7 (5.0-8.7)	4.4 (3.1-6.1)	10.4 (8.4-12.8)	11.8 (9.4-14.8)
		456	212	50	67	43	99	106
16-17	782	47.7 (43.4-52.0)	23.8 (20.7-27.1)	9.5 (7.3-12.2)	5.2 (3.7-7.3)	5.6 (4.0-7.8)	12.6 (9.9-15.9)	13.4 (10.8-16.5)
		375	204	68	42	48	93	99

NOTE. CI, confidence interval

Table S3. Regression estimates for associated factors with seropositivity for HPV-6, HPV Seroprevalence Study (n = 12,257, sera collected 2003-2006). NOTES. PR Prevalence Ratio, CI Confidence Interval, Ref Reference, $ Mutually adjusted for all other variables

	Crude PR (95%CI)	p-value	Fully adjusted PR (95%CI)[$]	p-value
Gender				
Female	Ref		Ref	
Male	1.1 (1.1-1.2)	0.001	1.2 (1.1-1.3)	<0.001
Age group (years)				
1-3	Ref		Ref	
4-6	1.8 (1.5-2.1)	<0.001	1.7 (1.4-2.0)	<0.001
7-9	1.6 (1.4-1.9)	<0.001	1.5 (1.3-1.8)	<0.001
10-11	1.6 (1.3-1.9)	<0.001	1.5 (1.2-1.7)	<0.001
12-13	1.2 (1.0-1.4)	0.133	1.1 (0.9-1.3)	0.604
14-15	1.0 (0.8-1.2)	0.910	0.9 (0.8-1.1)	0.514
16-17	0.9 (0.7-1.1)	0.199	0.8 (0.7-1.0)	0.105
Region of Residence				
West Germany	Ref		Ref	
East Germany	0.8 (0.7-0.9)	<0.001	0.8 (0.7-0.9)	0.001
Urbanity				
Rural	Ref		Ref	
Small City	1.2 (1.0-1.4)	0.041	1.1 (1.0-1.3)	0.107
Medium Sized City	1.1 (0.9-1.3)	0.211	1.1 (0.9-1.2)	0.446
Large City	1.2 (1.0-1.4)	0.037	1.2 (1.0-1.4)	0.038
Socioeconomic status of parents			ns#	
Low	Ref			
Middle	1.0 (0.9-1.1)	0.448		
High	1.0 (0.9-1.1)	0.625		
Migratory background of parents			ns#	
None	Ref			
One parent	1.1 (1.0-1.3)	0.085		
Both parents	1.2 (1.0-1.3)	0.005		
Number of household members			ns#	
	1.1 (1.1-1.1)	<0.001		
Number of siblings in household				
	1.1 (1.1-1.1)	<0.001	1.1 (1.1-1.1)	<0.001
BMI			ns#	
	1.0 (1.0-1.0)	<0.001		

NOTES. PR Prevalence Ratio, CI Confidence Interval, Ref Reference, $ Mutually adjusted for all other variables in the model, #ns= Variables were not significantly associated with HPV seroprevalence in the final model and therefore excluded

Table S4. Regression estimates for associated factors with seropositivity for HPV-11, HPV Seroprevalence Study (n = 12,257, sera collected 2003-2006).

	Crude PR (95%CI)	p-value	Fully adjusted PR (95%CI)[$]	p-value
Gender				
Female	Ref			
Male	1.0 (0.8-1.3)	0.879	ns[#]	
Age group (years)				
1-3	Ref		Ref	
4-6	1.6 (1.1-2.4)	0.021	1.6 (1.0-2.4)	0.030
7-9	1.4 (1.0-2.1)	0.072	1.4 (0.9-2.0)	0.111
10-11	1.3 (0.8-2.0)	0.318	1.2 (0.7-1.9)	0.502
12-13	0.8 (0.5-1.3)	0.372	0.8 (0.5-1.2)	0.262
14-15	0.7 (0.4-1.2)	0.201	0.7 (0.4-1.2)	0.161
16-17	0.7 (0.4-1.1)	0.141	0.7 (0.4-1.2)	0.189
Region of Residence				
West Germany	Ref		Ref	
East Germany	0.6 (0.5-0.9)	0.007	0.7 (0.5-0.9)	0.021
Urbanity			ns#	
Rural	Ref			
Small City	1.4 (0.9-2.1)	0.166		
Medium Sized City	1.2 (0.7-1.8)	0.542		
Large City	1.6 (1.0-2.5)	0.058		
Socioeconomic status of parents			ns#	
Low	Ref			
Middle	1.1 (0.9-1.5)	0.371		
High	1.2 (0.9-1.6)	0.270		
Migratory background of parents			ns#	
None	Ref			
One parent	0.9 (0.6-1.5)	0.674		
Both parents	1.1 (0.9-1.5)	0.405		
Number of household members				
	1.1 (1.1-1.2)	0.002	1.1 (1.0-1.2)	0.043
Number of siblings in household			ns#	
	1.1 (1.0-1.2)	0.053		
BMI			ns#	
	1.0 (0.9-1.0)	0.004		

NOTES. PR Prevalence Ratio, CI Confidence Interval, Ref Reference, $ Mutually adjusted for all other variables in the model, #ns= Variables were not significantly associated with HPV seroprevalence in the final model and therefore excluded

Table S5. Regression estimates for associated factors with seropositivity for HPV-18, HPV Seroprevalence Study (n = 12,257, sera collected 2003-2006).

	Crude PR (95%CI)	p-value	Fully adjusted PR (95%CI)[$]	p-value
Gender			ns[#]	
Female				
Male	1.2 (1.0-1.5)	0.095		
Age group (years)			ns#	
1-3	Ref			
4-6	0.8 (0.5-1.3)	0.463		
7-9	0.9 (0.6-1.3)	0.650		
10-11	0.7 (0.5-1.2)	0.182		
12-13	0.9 (0.6-1.4)	0.707		
14-15	1.0 (0.7-1.4)	0.800		
16-17	1.2 (0.8-1.7)	0.421		
Region of Residence				
West Germany	Ref		Ref	
East Germany	0.7 (0.5-1.0)	0.055	0.7 (0.5-1.0)	0.033
Urbanity				
Rural	Ref		Ref	
Small City	0.9 (0.6-1.2)	0.466	0.8 (0.6-1.2)	0.320
Medium Sized City	0.7 (0.5-1.0)	0.069	0.7 (0.4-1.0)	0.041
Large City	0.9 (0.6-1.3)	0.421	0.8 (0.6-1.2)	0.381
Socioeconomic status of parents			ns#	
Low	Ref			
Middle	1.1 (0.9-1.5)	0.359		
High	0.9 (0.7-1.2)	0.407		
Migratory background of parents			ns#	
None	Ref			
One parent	1.2 (0.8-1.8)	0.451		
Both parents	0.9 (0.6-1.3)	0.523		
Number of household members			ns#	
	1.0 (0.9-1.1)	0.985		
Number of siblings in household			ns#	
	1.0 (0.9-1.2)	0.707		
BMI			ns#	
	1.0 (1.0-1.0)	0.399		

NOTES. PR Prevalence Ratio, CI Confidence Interval, Ref Reference, $ Mutually adjusted for all other variables in the model, #ns= Variables were not significantly associated with HPV seroprevalence in the final model and therefore excluded

tropism	mucosal								cutaneous						
risk groups (IARC)	HR						LR								
genus	α								β				γ	μ	ν
species	α9				α7		α10		α2	β1	β2	β3	γ1	μ1	ν1
type	31	33	52	58	16	18	45	6	11	10	8	38	49	4	1	41
vaccine-relevance	9-val.														
					4-val.			4-val.							
					2-val.										

Figure S1. Selection criteria of HPV types

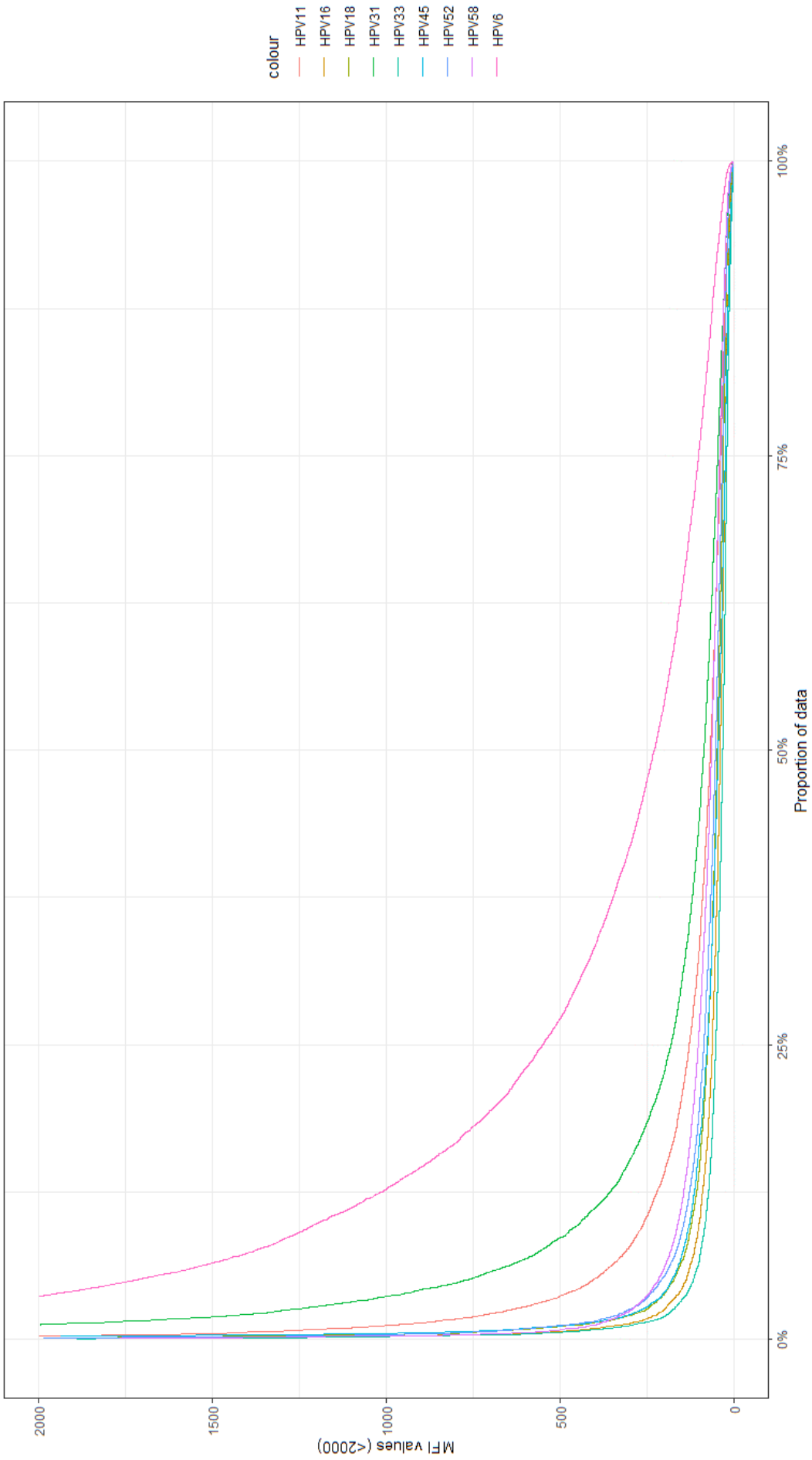

Figure S2. Percentile plot of the antibody reaction (MFI values) of mucosal HPV types HPV-6, HPV-11, HPV-16, HPV-18, HPV31, HPV33, HPV45, HPV52, HPV58, HPV Seroprevalence Study (n = 12,257, sera collected 2003-2006)

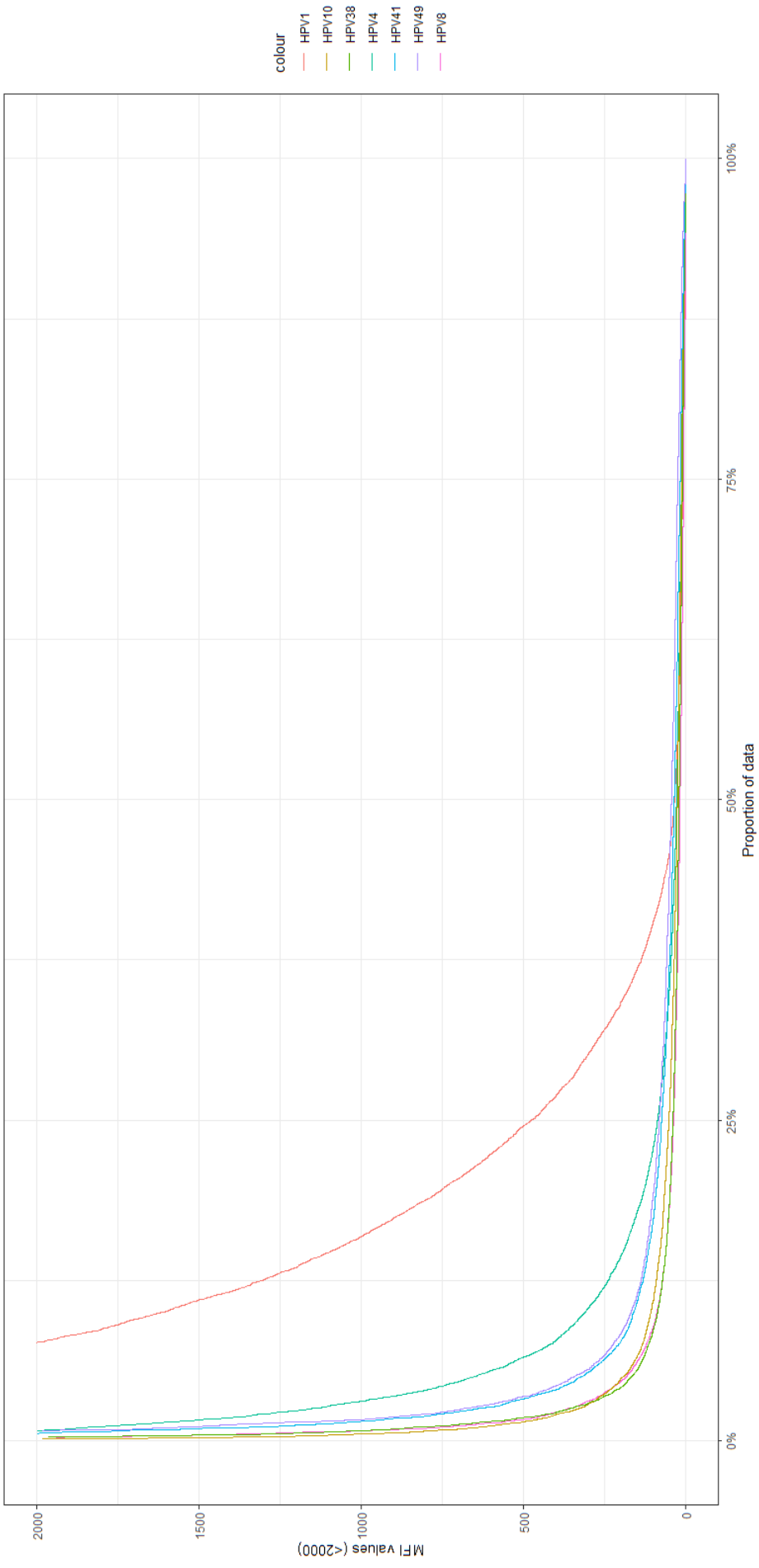

Figure S3. Percentile plot of the antibody reaction (MFI values) of cutaneous HPV types HPV1, HPV4, HPV8, HPV10, HPV38, HPV41, HPV49, HPV Seroprevalence Study (n = 12,257, sera collected 2003-2006).

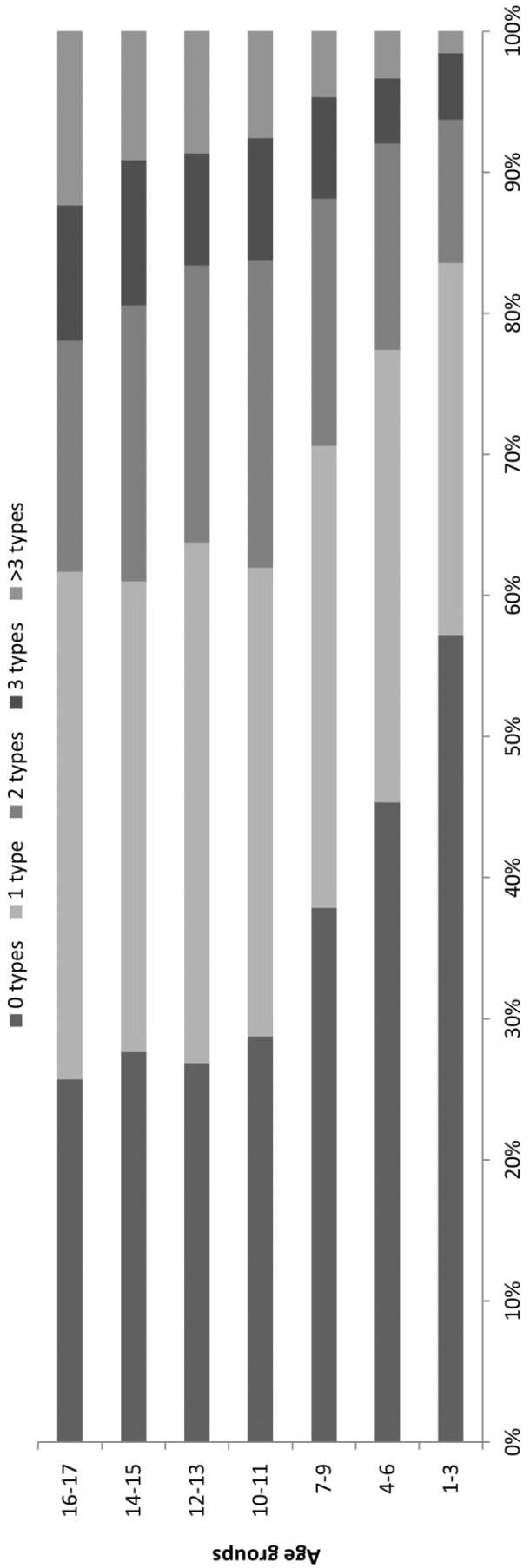

Figure S4. Multiple HPV seropositivity by age, HPV Seroprevalence Study (n = 12,257, sera collected 2003-2006).

6. LEBENSLAUF

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

7. PUBLIKATIONSLISTE

PUBLIKATIONEN IN WISSENSCHAFTLICHEN ZEITSCHRIFTEN MIT PEER-REVIEW VERFAHREN

2022

Loenenbach, A., Pawlita, M., Waterboer, T., Poethko-Müller, C., Thamm, M., Harder, T., Wichmann, O., Wiese-Posselt, M. Seroprevalence of mucosal and cutaneous Human Papillomavirus (HPV) types among children and adolescents in the general population in Germany. BMC Inf Dis, 2022. doi: 10.1186/s12879-022-07028-8. Impact factor: 3,090 für 2020 (Quelle: Journal Citation Reports).

2021

Loenenbach, A., Markus, I., Lehfeld, A., an der Heiden, M., Haas, W., Kiegele, M., Ponzi, A., Unger-Goldinger, B., Weidenauer, C., Schlosser, H., Beile, A., Buchholz, U. SARS-CoV-2 variant B.1.1.7 susceptibility and infectiousness of children and adults deduced from investigations of childcare centre outbreaks, Germany, 2021. Euro Surveill. 2021 May;26(21):2100433. doi: 10.2807/1560-7917.ES.2021.26.21.2100433. Impact factor: 6,307 für 2020 (Quelle: Journal Citation Reports).

2020

Loenenbach, A., van der Ende, A., de Melker, H., Sanders, E., Knol, M. The clinical picture and severity of invasive meningococcal disease serogroup W compared with other serogroups in the Netherlands, 2015-2018. Clin Infect Dis. 2020, May 6; 70(10):2036-2044. doi: 10.1093/cid/ciz578. Impact factor: 9,079 für 2020 (Quelle: Journal Citation Reports).

2019

Loenenbach, A., Poethko-Müller, C., Pawlita, M., Thamm, M., Harder, T., Waterboer, T., Deleré, Y., Wichmann, O., Wiese-Posselt, M. Mucosal and cutaneous Human Papillomavirus seroprevalence among adults in the prevaccine era in Germany - Results from a nationwide population-based survey. Int J Infect Dis. 2019 Mar 20;83:3-11. doi: 10.1016/j.ijid.2019.03.022. Impact factor: 3,202 für 2019 (Quelle: Journal Citation Reports).

2018

Loenenbach, A., Beulens, C., Euser, S., van Leuken, J., Bom, B., van der Hoek, W., de Roda Husman, A., Ruijs, W., Bartels, A., Rietveld, A., den Boer, J., Brandsema, P. Two Community Clusters of Legionnaires' Disease Directly Linked to a Biologic Wastewater Treatment Plant, the Netherlands. Emerg Infect Dis, 2018. 24(10): p. 1914-1918. Impact factor: 7,185 für 2018 (Quelle: Journal Citation Reports).

Lachmann, R., **Loenenbach, A**., Waterboer, T., Brenner, N., Pawlita, M., Michel, A., Thamm, M., Poethko-Muller, C., Wichmann, O. and Wiese-Posselt, M. Cytomegalovirus (CMV) seroprevalence in the adult population of Germany. PLoS One, 2018. 13(7): p. e0200267. Impact factor: 2,776 für 2018 (Quelle: Journal Citation Reports).

Buder, S., Dudareva, S., Jansen, K., **Loenenbach, A.**, Nikisins, S., Sailer, A., Guhl, E., Kohl, P.K., Bremer, V.; GORENET study group. Antimicrobial resistance of Neisseria gonorrhoeae in Germany: low levels of cephalosporin resistance, but high azithromycin resistance. BMC Infect Dis. 2018 Jan 17;18(1):44. doi: 10.1186/s12879-018-2944-9. Impact factor: 2,565 für 2018 (Quelle: Journal Citation Reports).

2016

Dudareva-Vizule, S., Buder, S., Jansen, K., **Loenenbach, A.**, Sailer, A., Guhl, E., Kohl, P., Bremer, V. Gonokokken-Resistenz-Netzwerk (GORENET): Grundlage für Überwachung der Neisseria-gonorrhoea-Antibiotikaresistenzen in Deutschland. Volume 14, Issue Supplement S3, 1–58. Journal of the German Society of Dermatology, 2016. Impact factor: 2,865 für 2016 (Quelle: Journal Citation Reports).

2015

Loenenbach, A., Dudareva-Vizule, S., Buder, S., Sailer, A., Kohl, P., Bremer, V. Laboratory practices: diagnostics and antibiotics resistance testing of Neisseria gonorrhoeae in Germany. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 58(8):866-74. 2015. Impact factor: 1,499 für 2015 (Quelle: Journal Citation Reports).

WEITERE PUBLIKATIONEN

2021

Loenenbach, A., Markus, I., Stauke, J., Michel, J., Nitsche, A., Unger-Goldinger, B., Weidenauer, C., Schlosser, H., Beile, A., Buchholz, U.: Positivenanteile, RNA-Kopien und Anzüchtbarkeit von Proben zum Isolationsende von SARS-CoV-2 VOC B.1.1.7 („Alpha“) positiven Fallpersonen; LK Bergstraße; März 2021. Epid Bull 2021; 25:14 - 18. doi: 10.25646/8681

Wöchentliche Ausgabe GrippeWeb-Wochenbericht seit Ausgabe: GrippeWeb-Wochenbericht Buchholz, U., Buda, S., **Loenenbach, A.**, Prahm, K., Preuß, U., Streib, V., Haas, W. GrippeWeb-Wochenbericht. Kalenderwoche 31 (02.08.2021 – 08.08.2021)., Datenstand: 10.08.2021. doi: 10.25646/8890

Loenenbach, A., Markus, I., Buchholz, U.: Empfänglichkeit und Infektiosität von Kindern und Erwachsenen bezüglich der SARS-CoV-2-Variante B.1.1.7, abgeleitet aus drei Ausbrüchen von Kindertagesstätten und sich daran anschließenden Haushaltssituationen; Landkreis Bergstraße, Februar/März 2021; In: Autorengruppe Corona-KiTa-Studie (2021). 4. Quartalsbericht der Corona-KiTa-Studie (II/2021). München 2021: DJI, online verfügbar unter: https://corona-kita-studie.de/quartalsberichte-der-corona-kita-studie.

2015

Loenenbach, A. Primärprävention in der Praxis (Beispiel der HPV-Impfung). MDK Forum. Das Magazin der Medizinischen Dienste der Krankenversicherung. Medizinischer Dienst des Spitzenverbandes Bund der Krankenkassen e.V. (MDS); Essen/Germany, 4/2015.

2014

Loenenbach, A., Dudareva-Vizule, S., Buder, S., Sailer, A., Kohl, P., Bremer, V. Diagnostik und Antibiotikaresistenztestung von Neisseria gonorrhoeae in Deutschland. Erste Ergebnisse des Gonokokken-Resistenz-Netzwerks (GORENET). Epid Bull 2014; 37: 365 - 369.

KONGRESSBEITRÄGE MIT PEER-REVIEW VERFAHREN

2019

Loenenbach A, Beulens C, Stip M, Götz HM. Posterpräsentation auf der ESCAIDE Konferenz (European Scientific Conference on Applied Infectious Disease Epidemiology) 2019. "Piloting an algorithm to guide clinical treatment decisions among notified partners of men having sex with men (MSM) with syphilis in Rotterdam, the Netherlands". Stockholm, Schweden, 2019.

Loenenbach A, Beulens C, Stip M, Götz HM. Posterpräsentation auf dem STI & HIV Weltkongress 2019 (STI & HIV World Congress - Joint Meeting of the 23rd ISSTDR and 20th IUSTI). „Piloting an algorithm to guide clinical treatment decisions among notified partners of syphilis-positive men who have sex with men". Vancouver, Kanada, 2019.

Loenenbach, A., van der Ende, A., de Melker, H., Sanders, E., Knol, M. Mündliche Präsentation auf dem 15. Europäischen Meningokokken Kongress (Congress of The European Meningococcal and Haemophilus Disease Society (EMGM)). "The clinical picture and severity of invasive meningococcal disease serogroup W compared with other serogroups in the Netherlands, 2015-2018". Lisbon, Portugal, 2019.

2018

Loenenbach, A., Beulens, C., Euser, S., van Leuken, J., Bom, B., van der Hoek, W., de Roda Husman, A., Ruijs, W., Bartels, A., Rietveld, A., den Boer, J., Brandsema, P. Posterpräsentation auf dem 28. Transmissionstag Symposium (Transmissiedag symposium). "A biological wastewater treatment plant as a probable direct source for two community clusters of Legionnaires' disease in the Netherlands, 2016-2017". Amersfoort, Niederlande, 2018.

Loenenbach, A., van der Ende, A., de Melker, H., Sanders, E., Knol, M. Mündliche Präsentation auf der ESCAIDE Konferenz (European Scientific Conference on Applied Infectious Disease Epidemiology) 2018. "The severity and clinical manifestation of invasive meningococcal serogroup W disease in comparison to other serogroups in the Netherlands". St. Julian's, Malta, 2018.

Loenenbach, A., van der Ende, A., de Melker, H., Sanders, E., Knol, M. Mündliche Präsentation auf der Nationalen WEON Konferenz (Netherlands Epidemiological Conference) 2018. „Ongoing Increase of invasive serogroup W meningococcal disease with high case fatality in the Netherlands". Bilthoven, Niederlande, 2018.

2017

Loenenbach, A., Poethko-Müller, C., Pawlita, M., Thamm, M., Harder, T., Waterboer, T., Deleré, Y., Wichmann, O., Wiese-Posselt, M. Mündliche Präsentation auf der 31. Internationalen Papillomavirus Konferenz (31st Annual International Papillomavirus Conference & Clinical Workshops). „Prevalence of 19 human papillomavirus (HPV) types in a nationwide representative cross-sectional survey in Germany in the pre-vaccine era". Kapstadt, Südafrika, 2017.

2016

Loenenbach, A., Poethko-Müller, C., Pawlita, M., Thamm, M., Harder, T., Waterboer, T., Deleré, Y., Wichmann, O., Wiese-Posselt, M. Posterpräsentation auf der EUROGIN Konferenz (European Research Organisation on Genital Infection and Neoplasia) 2016: „Prevalence of 19 human papillomavirus (HPV) types in a nationwide representative cross-sectional survey in Germany in the pre-vaccine era". Salzburg, Österreich, 2016.

Loenenbach, A., Poethko-Müller, C., Pawlita, M., Thamm, M., Harder, T., Waterboer, T., Deleré, Y., Wichmann, O., Wiese-Posselt, M. Mündliche Präsentation auf dem Deutschen STI-Kongress 2016: „Seroprävalenzen von 19 Humanen Papillomviren (HPV)-Typen repräsentativ für die deutsche Bevölkerung vor Einführung der HPV-Impfung". Berlin, Deutschland, 2016.

Schröter, J., Michel, A., **Loenenbach, A.**, Kuhnert, R., Poethko-Müller, C., Wichmann, O., Thamm, M., Wiese-Posselt, M., Pawlita, M. and Waterboer, T. Antibody response to and risk factors for Helicobacter pylori infection in a German cross-sectional population-based study. Posterpräsentation auf der 13. Internationalen Konferenz zu Molekularer Epidemiologie (International Conference on Molecular Epidemiology and Evolutionary Genetics of Infectious Diseases), Antwerpen, Belgien, 2016.

2015

Dudareva-Vizule, S., Buder, S., Jansen, K., **Loenenbach, A.**, Nikisins, S., Sailer, A., Guhl, E., Kohl, P., Bremer, V. Posterpräsentation auf dem STI & HIV Weltkongress 2015 (STI & HIV World Congress 2015): Antimicrobial resistance of Neisseria gonorrhoea in Germany, results from the gonococcal resistance network (GORENET). Sexually Transmitted Infections 91(Suppl 2): A111.2-A112.

2014

Loenenbach, A., Dudareva-Vizule, S., Buder, S., Sailer, A., Kohl, P., Bremer, V. Posterpräsentation auf dem Deutschen STI-Kongress 2014: „Die deutsche Laborlandschaft zu Diagnostik und Resistenzbestimmung bei Neisseria gonorrhoeae – Ergebnisse der ersten Phase des Gonokokken-Resistenz Netzwerks (GORENET)". Berlin, Deutschland, 2014.

Loenenbach, A., Dudareva-Vizule, S., Buder, S., Sailer, A., Kohl, P., Bremer V. Abstract Konferenzband. The German Laboratory Diagnosis and Resistance Screening in Neisseria gonorrhoeae - Results of the first Phase of Gonococcal-Resistance Networks (GORENET), 2014, Journal der Deutschen Dermatologischen Gesellschaft 12(10):981-982.

2013

Dudareva-Vizule, S., **Loenenbach, A.**, Buder, S., Sailer, A., Kohl, P., Hamouda, O., Bremer, V. Konferenzbeitrag auf der 65. Jahrestagung der Deutschen Gesellschaft für Hygiene und Mikrobiologie (65th Annual Meeting of the German Society for Hygiene and Microbiology), Rostock, Deutschland, 2013. International journal of medical microbiology, IJMM Conference: Volume: 303.

8. DANKSAGUNG

Ich möchte mich bei meinem Doktorvater PD Dr. Ole Wichmann sowie bei meinen Betreuenden Dr. Miriam Wiese-Posselt und Dr. Thomas Harder für ihre großartige und langjährige Unterstützung bei der Durchführung dieser Arbeit bedanken. Ich möchte mich für ihre außerordentliche Ausdauer bedanken, meine Promotion trotz meiner 2,5-jährigen Exkursion im Rahmen meines EPIET-Fellowships weiterhin zu betreuen und mit Hilfe derer sie mich darüber hinaus auch immer motiviert haben, trotz der zahlreichen Herausforderungen, die das Projekt und die Publikationen mit sich brachten, die Arbeit schließlich fertigzustellen.

Weiterhin gilt mein Dank den Koautor*innen der drei Publikationen für die gute und konstruktive Zusammenarbeit. Hierbei möchte ich mich insbesondere bei Dr. Tim Waterboer, Dr. Michael Pawlita und dem gesamten Labor-Team der Abteilung Molekulare Diagnostik onkogener Infektionen des Deutschen Krebsforschungszentrums in Heidelberg für die Offenheit, die wichtige inhaltliche Unterstützung, den fachlichen Austausch, die hervorragende Arbeit im Labor und nicht zuletzt die Möglichkeit meiner Studienaufenthalte in Heidelberg am DKFZ sowie in St. Ulrich bedanken.

Mein Dank gilt auch Dr. Christina Poethko-Müller und Dr. Michael Thamm von der Abteilung für Epidemiologie und Gesundheitsmonitoring am RKI für die wissenschaftliche Begleitung und die Beantwortung meiner vielen Fragen zu den beiden Bevölkerungsstudien.

Ferner gilt mein Dank den zahlreichen Studienteilnehmenden von KiGGS und BGS, ohne deren Beitrag diese und viele weitere Projekte zur Beantwortung epidemiologischer Fragestellungen zur Gesundheit der Bevölkerung nicht möglich wären.

Dank gilt auch meiner Kollegin und Koautorin Raskit Lachmann, nicht zuletzt für den wichtigen Austausch gerade in vorpandemischen Zeiten.

Des Weiteren möchte ich mich bei meinen Eltern bedanken, die mir das Privileg ermöglichten, in einer Umgebung aufzuwachsen, in der es genügend Fürsorge, Ressourcen und Unterstützung gab, um den Weg (inklusive aller Umwege) einzuschlagen, den ich schließlich gegangen bin.

Zu guter Letzt möchte ich Christian danken, der mich auf diesen vielen (Um-)Wegen immer begleitet und unterstützt hat.