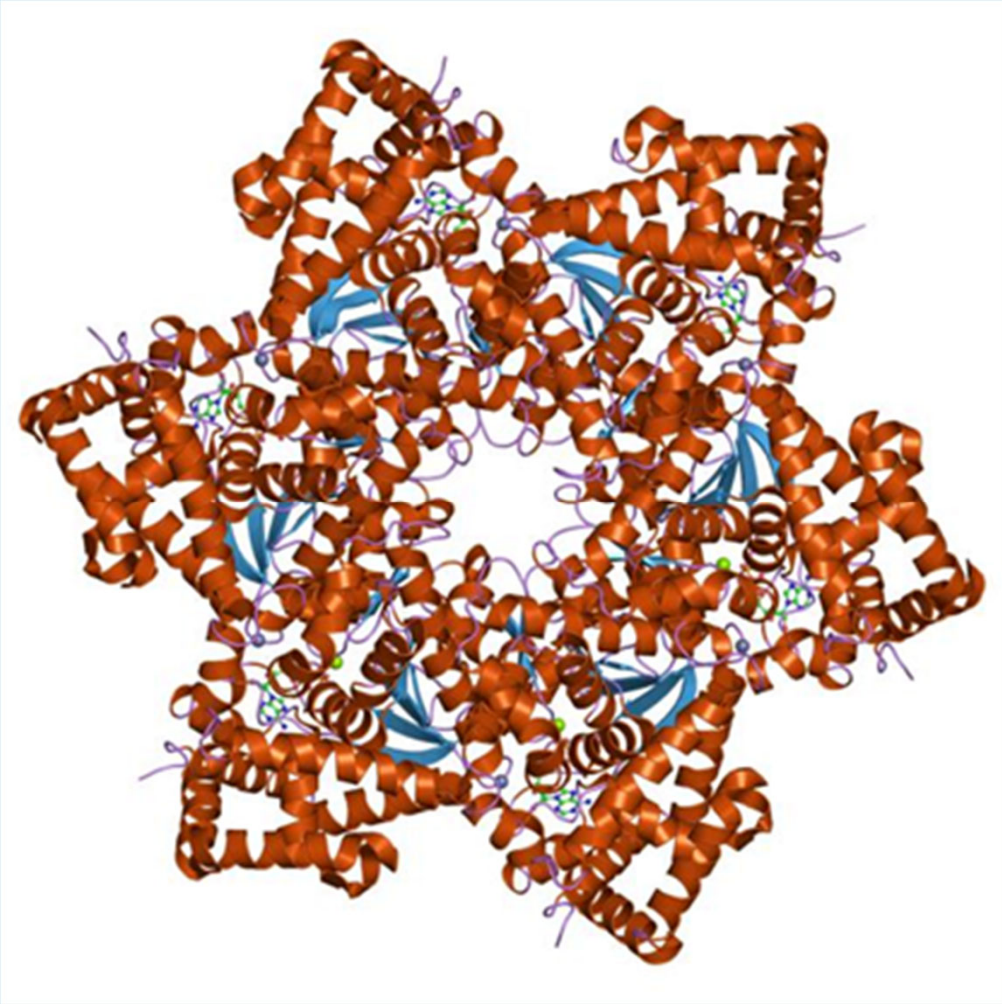
AKERSHUS UNIVERSITETSSYKEHUS

HPV i kirurgisk røyk. Lukten av faren eller slag i luften ?



Mireille Wulf
Smittevernoverlege Ahus

Innhold

- Om Human papilloma virus
- HPV & kirurgisk røyk
- Vaksinasjon
- Policy i andre land
- Diskusjon

Human papilloma virus

- ✓ Papovaviridae
  - ✓ DNA virus uten menbrankappe (non-enveloped)
  - ✓ 55 nm i diameter
  - ✓ Kapsid 2 proteiner: L1, L2

- ✓ Mer en 200 typer
- ✓ Celleforandringer : fra vorter til kreft
- ✓ Kan ikke dyrkes i cellekulturer

- ✓ Rund 42 mucosale / genitale typer

Abul Bajandar from Bangladesh

Tree man syndrome
Epidermydodysplasia verruciformis (HPV 5, 8)

Kreftassosierte mucosale HPV typer - gradering

Risikogruppe	HPV-genotype
Høyrisiko	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Sannsynlig høyrisiko	68
Mulig høyrisiko	26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85, 97
Lavrisiko	6, 11, 40, 42, 43, 44, 54, 61, 71, 72, 81, 84, 89

HPV – mukosale infeksjoner

- Vanligvis uten symptomer
- over 90% går infeksjonen over av seg selv etter ½ - 1 ½ år
- virus kan være i dvale : intermediate shedding

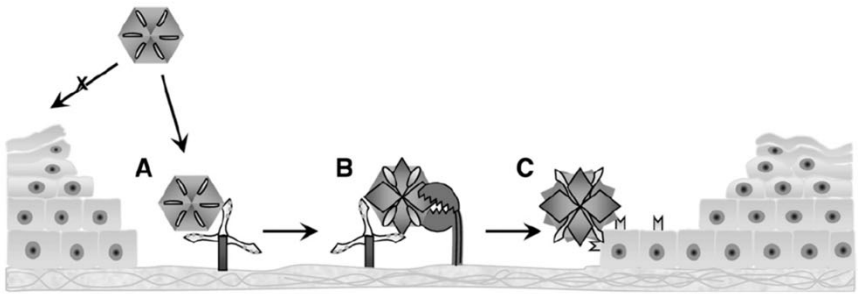


Fig. 1. The virion first binds to HSPGs on the BM exposed after disruption (A). This induces a conformational change exposing a site on L2 susceptible to proprotein convertase (furin or PC 5/6) cleavage (B). After L2 cleavage, an L2 neutralizing epitope is exposed and a previously unexposed region of L1 binds to an unidentified secondary receptor on the invading edge of the epithelial cells (C). BM = basement membrane; HSPG = heparan sulfate proteoglycan.

Review

Current understanding of the mechanism of HPV infection

John T. Schiller *, Patricia M. Day, Rhonda C. Kines

Laboratory of Cellular Oncology, National Cancer Institute, Bethesda, MD 20892, USA

Human papillomavirus prevalence and type distribution in urine samples from Norwegian women aged 17 and 21 years: A nationwide cross-sectional study of three non-vaccinated birth cohorts

Tor Molden [a,*], Berit Feiring [a], Ole Herman Ambur [b], Irene K. Christiansen [b], Mona Hansen [b], Ida Laake [a], Roger Meisal [b], Ellen Myrvang [b], Christine Monceyron Jonassen [b,c,1,2], Lill Trogstad [a,1]

Table 1.. HPV prevalence in urine samples from Norwegian women by birth cohort.

	21 yr 1990 (N=1565)		17 yr 1994 (N=5468)		17 yr 1996 (N=5894)	
HPV	**n**	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**
Total[a]	710	45.4 (42.9–47.8)	1087	19.9 (18.8–20.9)	907	15.4 (14.5–16.3)
High-risk (HR)[b]	466	29.8 (27.5–32.0)	611	11.2 (10.3–12.0)	445	7.6 (6.9–8.2)
Probably HR[c]	129	8.2 (6.9–9.6)	174	3.2 (2.7–3.6)	173	2.9 (2.5–3.4)
Low-risk[d]	455	29.1 (26.8–31.3)	640	11.7 (10.9–12.6)	500	8.5 (7.8–9.2)
Vaccine types[e]	254	16.2 (14.4–18.1)	403	7.4 (6.7–8.1)	283	4.8 (4.3–5.3)
Multiple infection[f]	408	26.1 (23.9–28.2)	504	9.2 (8.5–10.0)	352	6.0 (5.4–6.6)

HPV 16, 18 : nearly half high risk types
HPV 6, 11 : 6 common, 11 rare

Påvisning DNA, point prevalence – ikke gjennomgåt inf!

Infections with HPV

- infections with up to nine high-risk HPV types have been reported in cervical samples from non-HIV patients (Munoz et al., 2004, Schmitt et al., 2010, Schmitt et al., 2013)
- infections with at least 2 types have been reported in patients with oropharyngeal cancers (D'Souza et al., 2007, Beachler et al., 2012).
- Infections with multiple high-risk HPV types may increase the progression of premalignant epithelial cells to severe dysplasia; for example, infection with more HPV types increases the progression of cervical intraepithelial neoplasia (CIN)1 to severe dysplasia, CIN3 (Spinillo et al., 2014).

HPV Klinikk

- Genitale vorter: 10% prevalens blant seksuelt aktive: 90% type 6,11
- Utvikler seg i 6-10 måneder etter infeksjon
- Laryngeal vorter : recurrent laryngeal papillomatosis (RRP)

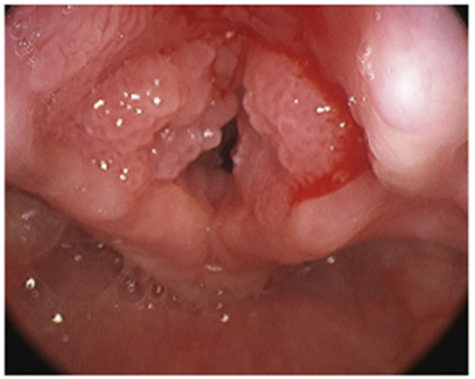


Fig. 1. Direct laryngoscopic view of pediatric larynx afflicted by RRP. Benign squamou epithelial proliferation is appreciable along laryngeal surface of epiglottis, bilateral aryepi glottic folds, false vocal folds, and true vocal folds.

- om lag 10 % en vedvarende infeksjon : risiko for kreftutvikling
    - Livmorhals : 70 % type 16,18
    - Anus, vulva, penis
    - Munn, svelg, øesofagus
    - Lung ? (multifaktoriell, patogenese uklar)

- Virus må ofte <u>integreres</u> i vertens DNA for at kreftutvikling skal finne sted.
- Kreft utvikling : etter 5-10 år, i gjennomsnitt mellom 20-25 år etter infeksjon (trenger **viral persistance**)

HPV - smittsommhet

'HPV er svært smittsomme' : men krever *intensiv nærkontakt*

- ✓ Seksuell overførbar: microabrasions allow viral entry into the basal cell layers of the mucosa
- ✓ Anogenital-anogenital eller anogenital-oral kontakt
- ✓ Vertikal smitte : fra mor-til-barn (gjennom placenta? Under fødsel?)
  - ✓ Anogenitale vorter, congenital conjuntival papilloma, juvenile (recurrent) laryngeal papillomatosis

Andre smittemåter uklare:

- ✓ Rolle av DNA på overflater ?
- ✓ Indirekte smitte gjennom hendene?
- ✓ Inhalering av partikler?

HPV og kirurgisk røyk

- Prosedyrer som danner kirurgisk røyk er ofte brukt ti å behandle pasienter med HPV sykdom
  - Loop electrical excision (LEEP) (gynekologiske ingrep)
  - Laser (vorter, kreft)
    - CO_2
    - APC, YAG, KTP
  - Elektrokoagulasjon
- Termisk desintegrasjon og fordamping av vev
- Kan inneholde levedyktige biologiske materialer
- Smitte risiko påvirket av
  - Mengde virus hos pasient
  - Hvor ofte er ansatte (mulig) eksponert
  - Forebyggende tiltak (sug, ventilasjon, åndedrettsvern, munnbind)

HPV – hvor stor er risikoen?

Risiko?

- Finns det smittsom HPV virus i røyk ?
- Blir ansatte smittet?
- Er vaksinasjon et effektivt tiltak ?

Systematic review

Human papillomavirus and surgical smoke: a systematic review

Andrew Fox-Lewis ,[1] Caroline Allum,[2] David Vokes,[3] Sally Roberts[4]

BMJ

Fox-Lewis A, *et al*. *Occup Environ Med* 2020;**77**:809–817. doi:10.1136/oemed-2019-106333

Review article

Airborne human papillomavirus (HPV) transmission risk during ablation procedures: A systematic review and meta-analysis

Stefano Palma [a], Timo Gnambs [b,c], Richard Crevenna [a], Galateja Jordakieva [a,*]

Environmental Research 192 (2021) 110437

HPV DNA i røyk?

- 14 studier : 10 påviser HPV DNA i kirurgisk røyk
  - Laser, LEEP
  - Forskjeller i test metodikk
  - Generelt : samme type i pasienter og i røyk (ikke alle er typert)

- Risikofaktor : avstand mellom sug og operasjonsområde (Zhou et al 2019)
- 2 studier (Bellina,1982; Kuchanak, 1996) indirekte testing: ingen indikasjon 'active biological material'

- 2 studier dyr modeller & laser kirurgi (Garden, 2002; Best, 2020)
  - Videre smitte av bovine / mus papillomavirus gjennom røyk
  - Obs: hudvorter, injeksjon prøvematerial i hud hos dyr – kan det sammenlignes med inhalering?

Kontaminering av ansatte gjennom røyk

- Ferenczy et al 1990
  - 1 kirurg, CO_2 laser, vorter & CIN lesioner
  - Ingen DNA påvist på slimhinnene
  - Røykavsug, brille, munnbindbruk

- Bergbrant et al 1994
  - laser kirurgi
  - 19 test episoder, antall individer?
  - Testing nese, nasolabial folds
  - 6 positive tester etter kirurgi – men 2 allerede positiv før operasjon

Weyandt 2011
- CO_2 laser
- to positive funn – men annen type HPV enn pasient
- Tilfeldig funn?

Illmarinen, 2012
- Ansatte involvert i behandling av 5 pasienter uretrale vorter, 5 laryngeal papillomatosis

- Samples fra munn slimhinnene og 'masks' = negativ
- Hansker testet positiv

Kontaminering av ansatte gjennom røyk

Cancer Management and Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Human papillomavirus DNA in surgical smoke during cervical loop electrosurgical excision procedures and its impact on the surgeon

Cancer Management and Research 2019:11 3643–3654

Zhou et al

International Archives of Occupational and Environmental Health (2021) 94:107–115
https://doi.org/10.1007/s00420-020-01568-9

ORIGINAL ARTICLE

Prevalence of HPV infections in surgical smoke exposed gynecologists

Xiaoli Hu[1] · Qingfeng Zhou[1] · Jian Yu[1] · Jing Wang[1] · Quanmei Tu[1] · Xueqiong Zhu[1]

Received: 5 October 2019 / Accepted: 25 August 2020 / Published online: 1 September 2020

Zhou et al

31 gynekologer, LEEP inngrep hos 134 pasienter

268 nasofarynx swabs :

- 134 preoperativt negativ
- 2 postoperativt positiv: 1 negativ etter 3 måneder, 1 etter 6 måneder

30% N95, 70% vanlig munnbind

Positive i gruppe som bruker vanlig munnbind

Hu et al

- 700 gynekologer
- Høyere forekomst i leger som driver med LEEP og/eller (?) elektrosurgery
- Most prevalent : HPV 16
- Svakhet : ingen multivariate analyse
- 45 av 82 fortsatt positiv etter 3 måneder
- 7 lost to follow up, 38 negativ etter 24 måneder
- No HPV relatert sykdom

Table 2 The correlation of positive rates in gynecologists who performed electrosurgery or not

	HPV testing		Total	χ^2	*P* value
	Positive	Negative			
Electrosurgery	42 (8.96%)	427 (91.04%)	469		
No electrosurgery	4 (1.73%)	227 (98.27%)	231		
Total	46 (6.57%)	654 (93.43%)	700	13.154	0.000

Table 3 The correlation of HPV-positive rates in gynecologists who performed LEEP or not

	HPV testing		Total	χ^2	*P* value
	Positive	Negative			
LEEP	36 (10.11%)	320 (89.89%)	356		
No LEEP	10 (2.91%)	334 (97.09%)	344		
Total	46 (6.57%)	654 (93.43%)	700	13.154	0.000

Table 6 The association between HPV detection rates and gynecologists operating LEEP according to age, operation time of electrosurgery, mask, smoke absorbing device and risk consciousness

From: Prevalence of HPV infections in surgical smoke exposed gynecologists

Factor	HPV testing in nasal swabs		Total	χ^2	*P* value
	Positive	Negative			
Age (years)				2.703	0.44
21–29	6 (6.38%)	88 (93.62%)	94		
30–39	20 (12.50%)	140 (87.50%)	160		
40–49	7 (8.97%)	71 (91.03%)	78		
≥ 50	3 (12.50%)	21 (87.50%)	24		
Operation time of electrosurgery (years)				10.149	0.017
$0 \le t < 5$	12 (6.94%)	173 (93.51%)	185		
$5 \le t < 10$	5 (7.94%)	58 (92.06%)	63		
$10 \le t < 15$	7 (15.22%)	39 (84.78%)	46		
≥ 15	12 (19.35%)	50 (80.65%)	62		
Surgical mask				30.891	0.000
No	7 (25.00%)	21 (75.00%)	28		
General mask	29 (16.20%)	150 (83.80%)	179		
N95 mask	0 (0%)	149 (100%)	149		
Smoke absorbing device				0.283	0.713
Yes	25 (10.73%)	208 (89.27%)	233		
No	11 (8.94%)	112 (91.06%)	123		
Risk consciousness				0.279	0.642
Yes	34 (9.94%)	308 (90.06%)	342		
No	2 (14.29%)	12 (85.71%)	14		

Hu et al 2021

HPV relaterte sykdom hos ansatte

- Halmo and Næss, 1991 : laryngeal papillomatosis, HPV 6 & 11
  - bruk av munnbind, hansker, øye beskyttelse
  - Ikke adekvat røyk avsug

- Calero and Brusis, 2003 : laryngeal papillomatosis
  - Gyn sykepleier, assistert i laser behandling og elektrosurgery uten 'adekvat' beskyttelsesutstyr
  - laryngeal papillomatosis anerkjent som 'occupational disease'

- Rioux et al, 2013 : two gynekologer med HPV 16 relaterte kreft i hals/munn
  - tonsil kreft
  - Tong svulst
  - Langt jobbing med laser & LEEP, eksponering mot røyk
  - Ingen bruk av munnbind eller åndedrettsvern, inadekvat røykavsug

Epidemiologi – høyere forekomst av HPV relatert sykdom hos helsepersonell?

2 studier basert på spørreundersøkelse

- Skiller ikke mellom hud eller slimhinne infeksjoner
- ((Rocco et al 1989 : høyere forekomst av vorter på hander i leger som jobber med laser behandling uten handskerbruk))
- Gloster et al 1995 :
  - forekomst av vorter hos kirurger som bruker CO2 laser 5,4% vs 4.9% i kontroll gruppe
  - Mulig økt forekomst av nasopharynx vorter (4/31= 13% vs 37/6124 = 0,6%)
  - men kritikk på kontroll gruppe som ble brukt

Forekomst av HPV ?

- Kofoed et al 2015: forekomst av HPV hos ansatte på gyn & dermat
- 4,4% HPV positiv i nasopharynx (11 ansatte, 4 med HPV 16 eller 18)
- Kommer overens med prevalens i samfunn

- Vanskelig å tolke mulig eksponering fordi cases er i flere grupper
- Forekomst av HPV relatert sykdom høyere i dermatology: vorter på hender etter 24 år

- Obs: selv rapportert prevalens av livmorhals dyplasi / kreft 12,5% (28/223). ???
- Sammenheng med smitteverntiltak kan ikke tolkes

Vaksiner – muligheter

- Cervarix
  - HPV 16 & 18
  - kryssbeskyttelse mot 18, 31, 33 (rund 80%)
  - Norges barnevaksinasjonsprogrammet fra 2017
  - Jenter (2009) og gutter (2018) 7. klassetrin & jenter født 1991 og senere (2016-2019)
- Gardasil
  - HPV 6, 11, 16 & 18
  - kryssbeskyttelse mot 18, 31, 33 (rund 70%)
  - Norges barnevaksinasjonsprogrammet til 2017

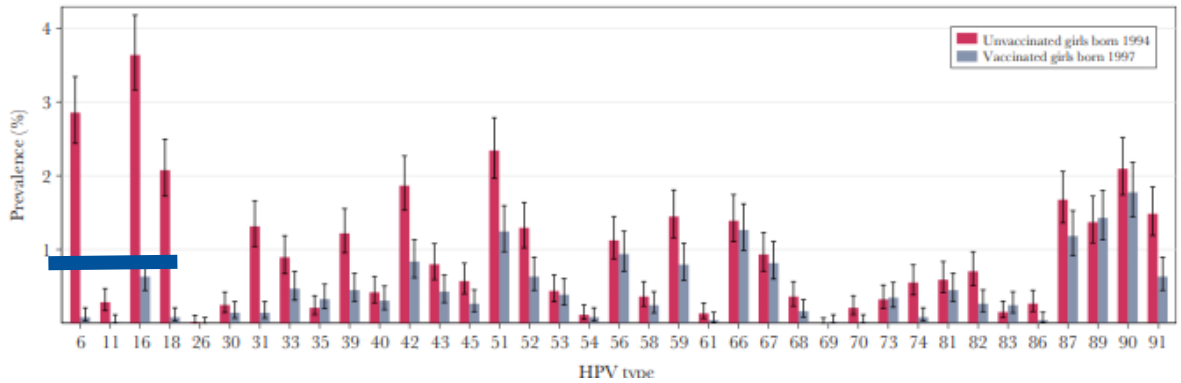
- Gardasil 9
  - HPV 6, 11, 16, 18, 31, 33, 45, 52 & 58

Substantial Decline in Prevalence of Vaccine-Type and Nonvaccine-Type Human Papillomavirus (HPV) in Vaccinated and Unvaccinated Girls 5 Years After Implementing HPV Vaccine in Norway

Berit Feiring,[1] Ida Laake,[1] Irene Kraus Christiansen,[2] Mona Hansen,[2] Jeanette Stålcrantz,[3] Ole Herman Ambur,[2,4,a] Per Magnus,[5] Christine Monceyron Jonassen,[6] and Lill Trogstad[1]

[1]Department of Infectious Disease Epidemiology and Modelling, Norwegian Institute of Public Health, Oslo, [2]Department of Microbiology and Infection Control, Akershus University

- The overall reduction of any HPV type was 42%, and the reduction in vaccine types was 81% in the vaccine cohort, as compared to the baseline cohort.
- The reduction of HPV-31/33/45 combined was 68%
- Prevalence of multiple infections high



Australia – Gardasil (4)

- 5-year report from Australia
- systematic HPV vaccination program
- quadrivalent vaccine was introduced in 2007 with greater than 80% uptake in girls and greater than 75% uptake in boys of at least 2 doses

- No new genital warts among vaccinated persons
- Recurrent respiratory pappilomatose annual incidence: decline from 0.16 to 0.02 per 100,000 children
- 15 incident cases noted nationwide; none of the mothers of these children were vaccinated.

Indicasjoner vaksinering

- Barnevaksinasjonsprogrammet: Folkehelseinstituttet har ikke anbefalinger om bruk av HPV-vaksine til personer som ikke inngår i vaksinasjonsprogram.

Other possible uses:

- Infection with a high risk HPV type: infections with multiple high-risk HPV types may increase the progression of premalignant epithelial cells to severe dysplasia
- the vaccine may be beneficial in treatment of patients with existing disease (laryngeal papillomatosis)
  - in reducing regrowth after debridement (longer interval between surgeries)
- CDC updated recommendations :
  - ACIP recommends vaccination for everyone through age 26 years if not adequately vaccinated when younger
  - For adults ages 27 through 45 years, clinicians can consider discussing HPV vaccination with people who are most likely to benefit

Why vaccinate older patients?

- Vaccine is less effective after acquisition of HPV
- Mean age at acquisition of causal HPV infection for cancers is unknown, but is estimated to be decades before cancer is diagnosed. In the USA oropharyngeal cancer highest disease burden now: median age 60-61
- individuals risk of infection might be different from the general populations: at any age, having a new sexual partner is a risk for acquiring a new HPV infection
- uncertainties about HPV natural history, such as prevalence of immunity after clearance of natural infections, and level of herd protection from the existing program
- some adults who are not adequately vaccinated might be at risk for new HPV infection and might benefit from
- **Current** knowledge: vaccines do not prevent progression of HPV infection to disease or treat HPV-related disease.

https://www.cdc.gov/mmwr/volumes/68/wr/mm6832a3.htm?s_cid=mm6832a3_w

Trenger vi å vaksinere ansatte?

Evidently Cochrane

Sharing health evidence you can trust

Ware L. "Teapots and unicorns: absence of evidence is not evidence of absence". Evidently Cochrane blog, 29 May 2020. https://www.evidentlycochrane.net/teapots-and-unicorns-absence-of-evidence-is-not-evidence-of-absence

"Teapots and unicorns: absence of evidence is not evidence of absence"

Take-home points

- It is pretty much impossible to prove a negative - that is, that something doesn't exist.
- Beware bold statements that something is ineffective or is no different to another treatment.
- There are many reasons why evidence may be unreliable.

Medisk etisk vurdering

autonomy (respecting the decisions of a competent health care worker) : kan ikke pålegges vaksinering pga uklar nytte verdi

benificience (doing good): uklar – men mulig stor på individ nivået

non-maleficience (doing no harm): påvirker dette etterlevelse av smitteverntiltak ?

justice (being fair and allocating resources equally) & utility (maximizing benefits and reducing harms to all concerned) :

Vaksiner er dyre, forebyggende tiltak bedre investering?

Hvem skal fa vaksine: nytteverdi høyere i noe andre (men vanskelig å definere)

Diskusjon

- Vi kan ikke utelukke at det fins smittsom HPV virus i kirurgisk røyk
- Vi kan ikke utelukke smitte mellom luft (kontakt?)

- Smitteverntiltak ser ut som å være effektivt (men ikke mye data:
  - Åndedrettsvern
  - Røykavsug
  - Ventilasjon
- Tiltak beskytter mot andre stoffer i kirurgisk røyk (men krever godt bruk / infrastructure)

- Vaksine kan beskytte for et enkelt individ – selv senere i livet enn barnevaksinsjons programmet