Primary HPV screening

Symposium VBS-GBS AP

15-6-2019

Kristof Cokelaere


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NOMINATIONS
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"BRILLIANT...THE BEST MOVIE ATTENBOROUGH HAS EVER MADE."
David Lewin - SUNDAY EXPRESS
"Superbly acted by Anthony Hopkins and Debra Winger..."
Derek Malcolm - THE GUARDIAN
RICHARD ATTENBOROUGH'S FILM
SHADOWLANDS
U

overview

- Disclosure
- Scientific debate
- Steps towards primary HPV testing in Belgium
- Current situation

Disclosure

Threats

- Implementation of HPV-based screening may induce loss of jobs and income in cytopathology laboratories. This serious socio-professional problem may be the source of a negative attitude among cyto-pathologists and cyto-technicians, professional lobbying against HPV

- Patholog

"This
not b

"... unfortunately, the contribution of current population screening to reducing cervical cancer mortality is very limited"

R. Verheijen -Gynecologic oncologist- in response to pathologists, Medisch contact 7-10-2015

"The pathologist profession is committed to limiting the incidence of cervical cancer with the help of microscopic examination of a cervical specimen. **I understand that Belgian pathologists are committed to maintaining this form of screening, which occupies an important part of the duties of a cyto-pathology laboratory.** I wish to show my sincere appreciation for this."

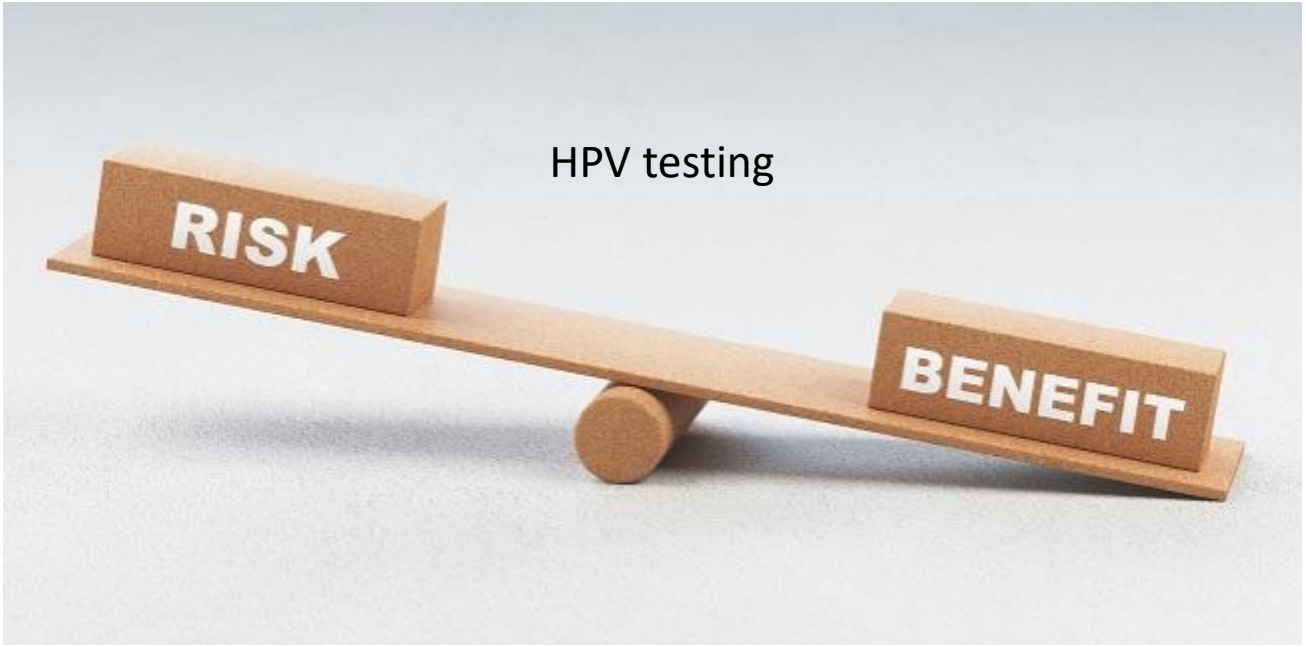
M. De Block in response to the CPA, 19-3-2019

E. Palkova, VVOG study day 6-6-19

Scientific debate

- HPV versus cytology = a story of benefits and harms
  - Ideal test = less cancer with fewer tests, less overtreatment and at lower cost

1. Overtreatment
2. Cost
3. Anxiety



HPV testing

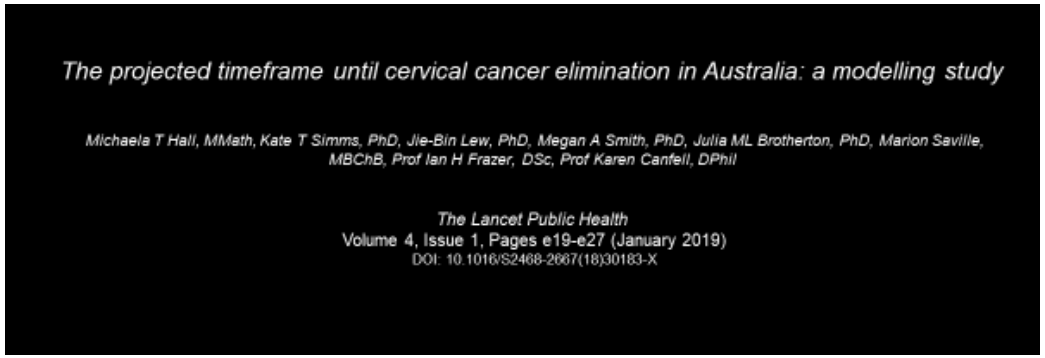
1. More effective
2. Safe

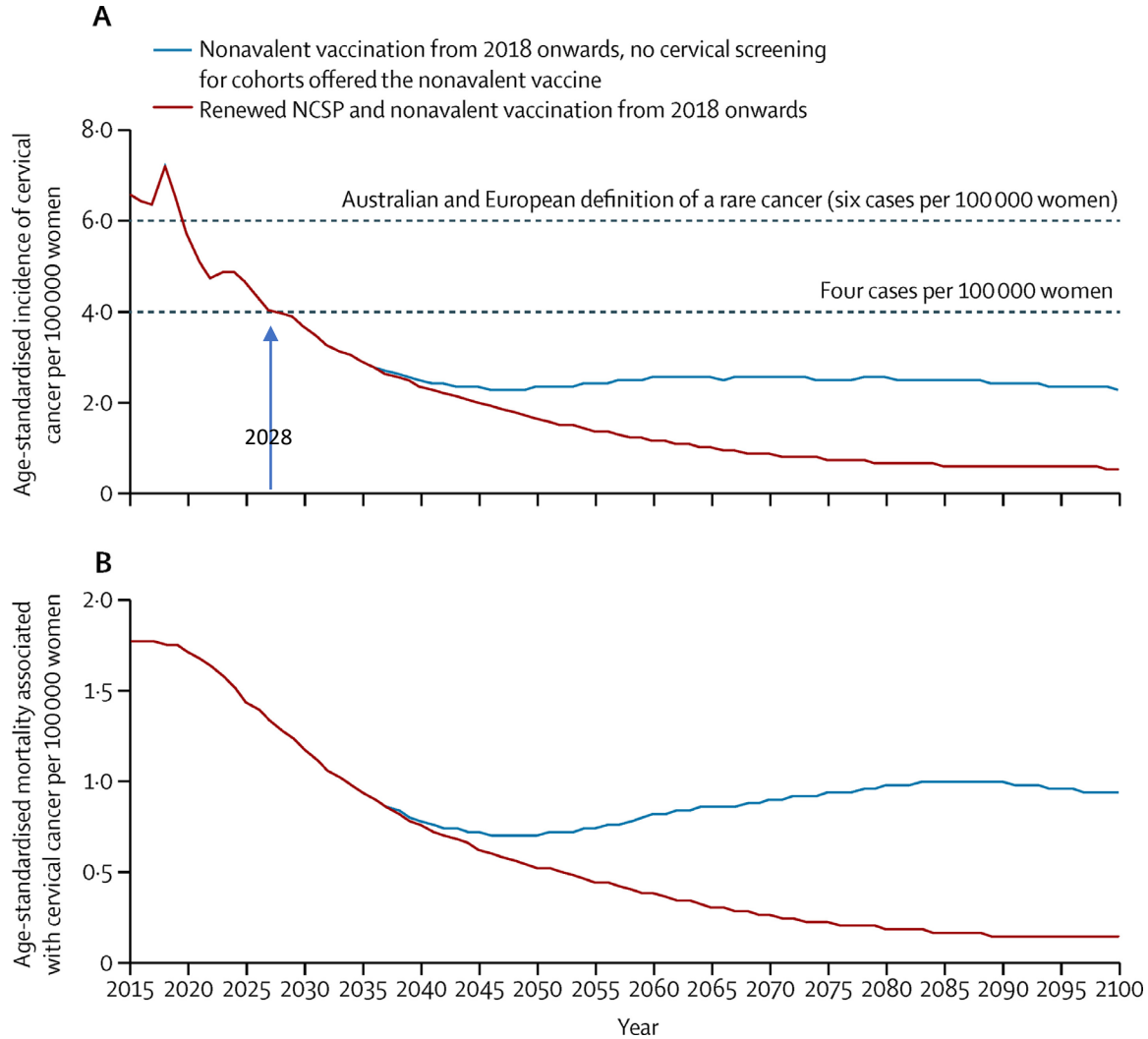
Scientific debate

- HPV testing detects more CIN2/CIN3
  - But causes more overtreatment (+ more anxiety) →doubling of colposcopy
    - Triage by cytology-(limited) genotyping-DSp16/KI67-methylation profile… ??
- Does HPV testing reduce the incidence of invasive cervical cancer ?
  - The debate on effectiveness is still open
- HPV negative invasive cervical cancer
  - How safe is HPV testing?

Australia & the Netherlands: The HPV fast and furious!

- Introduction of primary HPV screening
  - January 2017: the Netherlands
  - December 2017: Australia
- HPV vaccination
  - 2007: Australia (78% coverage)
  - 2010: the Netherlands (only 45% coverage in 2017!)
    - Belgium: 2009 (Flanders 90%, Walloon region 36%)
- Elimination of Cervical cancer





← Elimination treshold (from a public health point of view)

Modelling of effect by HPV vaccination and primary HPV testing

Huray! But the debate on effectiveness of HPV test re-opens… with nasty comments

"Inaccurate and fundamentally flawed analysis…

We are concerned that publication of their flawed study gives unwarranted credibility to spurious concerns based on simplistic modeling of non-representative data, potentially undermining public and provider confidence in a crucial cancer prevention policy."

M.A. Smith (MSAC) et al, letter to the editor (1 page and >1 page of disclosures) in response to an article on HPV screening by 2 NZ epidemiologists (J Am Soc Cytopathology 2018)

"Unfortunately, Smith et al invoke authority arguments that have no place in modern scientific discourse. The extent of consultation, the committee memberships listed … and who the authors have previously worked for, are completely irrelevant in a scientific discussion and mentioning them in this context raises concerns about scientific rigor."

B. Cox, M.J. Sneyd (epidemiologists University of Ontago, New Zealand)

Spoiling the party… by applying some basic epidemiology (Cox, Sneyd 2018)

- "Support for the Australian HPV primary screening policy comes from a simulation model that used the *detection sensitivity*… known to be <u>inappropriate</u> for the assesment of the public health impact of screening"

- "HPV screening 5-yearly was predicted to increase the annual incidence of cervical cancer in women screened to 121%...of current incidence after 10 years"
  - →"…an additional 222 women developing cervical cancer each year after 10 years".

- Note: epidemiologists questioning the *methodology* of the Australian modelling analysis (different conclusions using the same data-set)

HPV screening: effective? (Cox, Sneyd 2018)

- Detection sensitivity ≠ screening sensitivity
  - Example: PSA test detection sensitivity 84% but screening sensitivity 48%

  - Detection test sensitivity = **all** precursors (including those that do not progress → overdiagnosis)
    - "detecting disease that will regress … may be considered failure of screening"

  - Screening test sensitivity = detection of precursors that will progress
    - can only be tested by the **follow-up interval cancer method***

*avoids overdiagnosis bias

HPV screening: effective? (Cox, Sneyd 2018)

- HPV screening picks up more CIN2/CIN3 lesions, but…
- Purpose of screening = lower incidence of **invasive** cervical cancer
    - Endpoint of CIN2 (almost no progression) or CIN3 (only 1/3 progression) is not sufficient and mostly represents overdiagnosis

HPV screening: effective? (Cox, Sneyd 2018)

- Only 5 RCTs with reported invasive cervical cancer rates
  - 2/5 show **increased** incidence rate for invasive Cx cancer in HPV study arm

	Invasive cell carcinomas (n)					Total person-years	Median follow-up (years)	Time from enrolment	
	Total	1A*	>1A*	SCC	AC			≤2·5 years	>2·5 years
NTCC									
Experimental	9	8	1	8	1	242 984	5·1	8/117 300	1/125 684
Control	24	13	11	14	10	241 025	5·1	11/116 429	13/124 597
POBASCAM									
Experimental	20	7	13	15	5	198 525	9·0	12/54 970	8/143 555
Control	28	13	15	16	12	199 340	9·0	9/55 248	19/144 092
Swedescreen									
Experimental	5	3	2	4	1	75 477	12·0	0/15 590	5/59 887
Control	7	3	4	5	2	75 465	12·0	3/15 606	4/59 858
ARTISTIC									
Experimental	10	3	3	8	2	136 223	7·5	5/45 849	5/90 374
Control	4	3	1	3	1	45 376	7·5	4/15 266	0/30 109
Pooled									
Experimental§	44	21	19	35	9	653 209	6·6	25/233 709	19/419 500
Control§	63	32	31	38	25	561 206	6·2	27/202 549	36/358 656
All	107	53	50	73	34	1 214 415	6·5	52/436 258	55/778 156

Data are number of cases/person-years, unless otherwise stated. AC=adenocarcinoma. CIN=cervical intraepithelial neoplasia. SC
HPV arm. †Observations are censored 2·5 years after CIN2 or CIN3, if any. ‡Women younger than 30 years at enrolment were ex
randomisation ratios in studies.

	All randomised women			Women with negative test at entry*
	Overall	≤2·5 years from enrolment	>2·5 years from enrolment†	
NTCC	0·37 (0·17–0·80)	0·72 (0·29–1·80)	0·08 (0·01–0·58)	0·07 (0·01–0·56)
POBASCAM	0·72 (0·40–1·27)	1·34 (0·57–3·18)	0·42 (0·18–0·96)	0·36 (0·14–0·91)
Swedescreen	0·71 (0·23–2·25)	0·17 (0·01–3·33)	1·25 (0·34–4·65)	0·50 (0·09–2·73)
ARTISTIC	0·83 (0·26–2·66)	0·42 (0·11–1·55)	3·33 (0·18–60·98)	2·06 (0·10–41·19)
Pooled rate ratio (fixed effects)	0·60 (0·40–0·89)	0·79 (0·46–1·36)	0·45 (0·25–0·81)	0·30 (0·15–0·60)
I^2 (p for heterogeneity between studies)	0·0% (0·52)	12·3% (0·33)	56·8% (0·074)	21·4% (0·23)

Rate ratio (RR) = cancer detection rate in HPV arm versus cytology arm

Ronco, Arbyn et al (Lancet 2014): "HPV-based screening provides 60–70% greater protection against invasive cervical carcinomas compared with cytology"

Huh, Einstein et al. Interim clinical Guidance; Gynecologic Oncology 2015: *"….Of note, these results were primarily driven by the Italian and Dutch trials; no significant difference in cancer rates was observed in the Swedish and UK trials…"*

HPV screening: effective? (Cox, Sneyd 2018)

- "…the benefits regarding the prevention of invasive cervical cancer appear *less consistent*"

- "only the Finnish trial* measured the screening test sensitivity of HPV testing and cytology by this (*interval cancer*) method"
  - Screening test sensitivity: HPV 87% / Cytology 93%

*Malila et al (Int J Cancer 2013)

HPV screening: effective? (Cox, Sneyd 2018)

- “The evidence that the screening test sensitivity of the HPV test and cytology is similar suggests that the relative protection from invasive cervical cancer of HPV screening will also be similar to that of cytology”

- “a reduction in protection from cervical cancer by extending the screening interval from 2 years *(cytology)* to 5 years *(HPV)* is possible”

    - →+121% (222 women) each year (Australia)

Questioning the methodology of predictive models…

- KCE report 238a (Arbyn et al, 2015): provides a modelling analysis (similar to the Australian one) using **detection** test sensitivity
  - RR 0,45 = 60% reduction of invasive cancer with primary HPV testing
  - *'Less cancer cases at a lower cost'*

- The CPA has adressed this very same sensitivity issue and many other methodological biasses in a counter-report (june 2015)
  - →where are the –impartial- Belgian epidemiologists??

KCE report 238a: reaction by the Commission for Anatomic Pathology (33p)

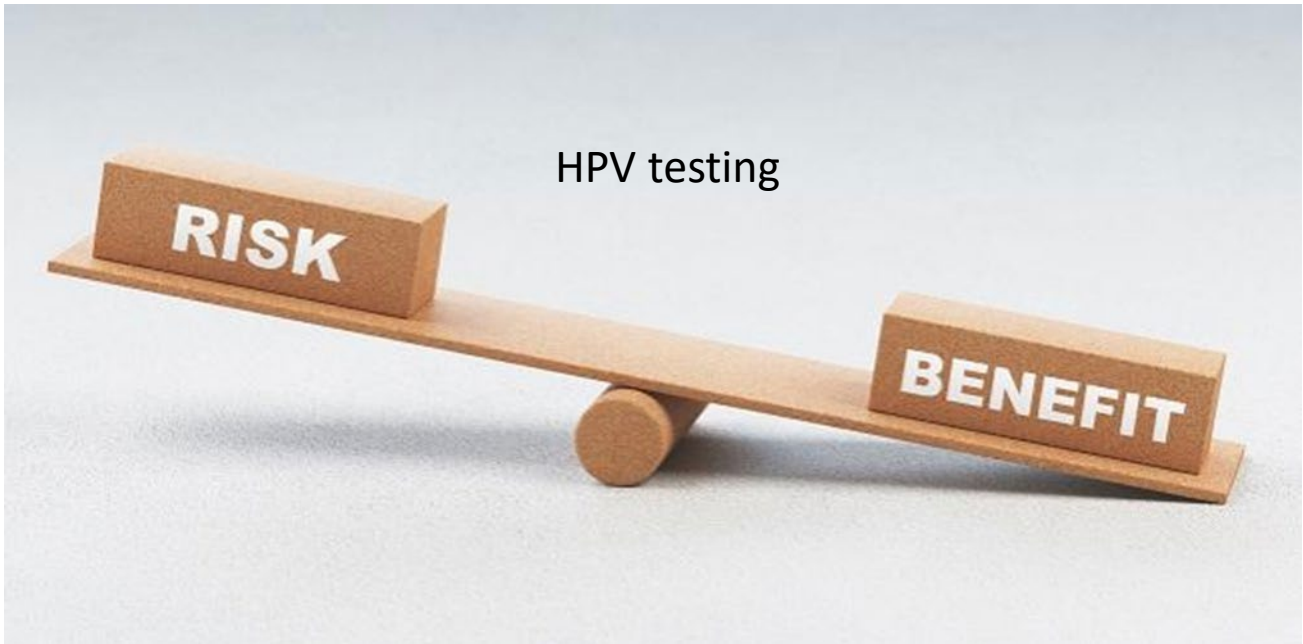
1. Increasing the participation rate in the target group (25-64 years) through the organization of a well-structured screening program is *absolutely necessary*
2. The "thin-layer technique" (LBC) must be refunded
3. **The predicted health benefits with primary HPV screening has not been proven in the Belgian context; the risks of over-treatment on the other hand are real***
4. Due to consecutive changes in nomenclature, 'over-screening' no longer exists.
5. The quality of the cytology screening in Belgium is high; great variability is seen however in the test results of the different HPV tests
6. **The KCE report predicted savings with primary HPV screening are highly uncertain due to the lack of correct parameterization of the theoretical model**.
7. There is no consensus with regards to the HPV test and algorithm to be used
8. The HPV vaccination program increases the risk of overtreatment with the use of a less specific (HPV) test
9. Due to lack of accurate data and insufficient in-depth analysis of the figures, the KCE report cannot serve as a policy document; it is to be considered a discussion document which needs to be further elaborated in consultation with the various health actors.

Preliminary results from the Netherlands: after 1 year of HPV testing there is a 9% drop in attendance (65% → 60%) and colposcopy rate x3!

(Folkert van Kemenade, VVOG study day 6-6-19)

1. Overtreatment (!)
2. Cost (?)
3. Anxiety (!)

HPV testing



1. More effective (?)
2. Safe

HPV-test: safe? What about HPV negative invasive cancer (‘interval cancer’)?

- 8/19 cancer cases (42%) in the Ronco-Arbyn analysis (Lancet 2014)
- 98/526 cancer cases (18,6%) in Blatt et al (Cancer Cytopathology 2015)
- 24/163 cancer cases (14,7%) in Flemish Cervibase (Feedback report 2017)

Conclusion in view of the scientific debate:

- M. Austin (2018):
  - “The use of models in health care decision making remains controversial”
  - “Replacement of cytology-based screening, medical history’s most effective cancer screening test, warrants the very highest level of evidence for clinical effectiveness”
  - “Validation of the Australian (*and Dutch*) simulation model’s predictions … will… be crucial in verifying the predictive claims…”
- Cox, Sneyd (2018):
  - “The principle of ‘first do not harm’ should apply in public health medicine”
  - “A more cautious approach to policy change would seem appropriate”

Steps towards primary HPV testing in Belgium

- January 2015 →KCE report 238a (Arbyn et al): ”HPV testing saves lives and money”
- March 2015 →M. Arbyn persuades NIHDI (RIZIV/INAMI) to refund primary HPV testing (within art. 32!)
- June 2015 →the CPA presents the counter-report to NIHDI; primary HPV testing is put ‘on hold’
- June 2016 →Cabinet employee* tries to persuade NIHDI to refund primary HPV testing (“end of 2017!” “public tender!”). After reaction by the CPA: still ‘on hold’

*according to Linkedin: 2007-2009 project manager with … (*HPV-company*) charged with ‘applying for reimbursment regulation for new medical tests in IVD’


OF COURSE YOU'RE BEING SWAMPED BY REGULATIONS, PAPERWORK AND ABSURD BUREAUCRACY...
YOU ASKED TO BE INTEGRATED INTO BELGIAN SOCIETY...
LECTRR

Steps towards primary HPV testing in Belgium

- September 2016 →The national Reference center for HPV is founded within WIV/ISP (now Sciensano)
- March 2017 → proposal to list primary HPV testing at the agenda of the Interministrial (8) Conference on Public Health end of 2017
- April 2017 →Minister Prévot suspends the activities of the Walloon Cervical Cancer Screening Working Group
  - ‘Le Ministre Prévot vient de nous adresser un courrier dans lequel il remercie les membres du groupe de travail pour l'analyse complète et claire de la problématique de la mise en place d'un programme de dépistage du cancer du col de l'utérus en Wallonie.
    > Malheureusement, "au vu du taux actuel de dépistages (du cancer du col) réalisé en Wallonie, et au vu des moyens budgétaires qui lui sont alloués" **il a décidé de ne pas mettre en place ce Programme de dépistage**. Il souhaite mettre la priorité sur une augmentation significative de la participation au programme dépistage du cancer colorectal’
- … (silence for >1 year, no consultations with health care providers, no questions)

Steps towards primary HPV testing in Belgium

- July 2018: **decision to switch to primary HPV screening** by the IMC on Public Health

1. the transition from screening of cervical cancer by cytology to screening by HPV test:
    - A cytological examination every three years for women between 25 and 29 years old
    - **HPV testing every 5 years** for women between 30 and 64 years old

2. the development of an action plan that describes the **implementation over a period of 2 years**, including investigating a tendering procedure and the budgetary implications of this transition

3. **limiting the performance of both HPV and cytology testing** within the framework of cervical cancer detection **to a minimum number of centers**

4. the selection of only one validated HPV test for cervical cancer detection, with the possibility of self-sampling provided.

5. propose measures to align the various tests with regard to cervical cancer with an evidence-based approach

6. the development of joint communication by the competent authorities for the information of the professional groups concerned (GPs, gynecologists, pathologists, laboratories, etc.) and the general public of the decision taken

The IMC instructs the IKW to coordinate with the experts and the technical working group of the IKW, the action plan by March 2019 to be submitted to the IMC

Steps towards primary HPV testing in Belgium

- September 2018 →Letter of the CPA to Min. De Block (only dutch version)
- …
- December 2018 → first meeting of the technical WG primary HPV testing (at Sciensano). Pathologists ask to include gynecologists
- …
- Beginning of March 2019 →Second attempt: Letter of the CPA to Min. De Block (dutch/french version) with cosignature of clinical biologists. Letter is sent to all healthcare ministers, head of FOD, NIHDI, patiënt representatives…

Concerne: Point de vue commun des anatomo-pathologistes et biologistes cliniques en matière de dépistage HPV primaire

Madame la Ministre,

nous recommandons unanimement de conserver l'actuel examen de dépistage (cytologie et test HPV reflex), de continuer à peaufiner le programme de dépistage du cancer du col de l'utérus récemment lancé en Flandres… Le changement éventuel de méthode de test (= switch en faveur du dépistage HPV primaire ou du co-testing) ne pourra être envisagé qu'ensuite et ce, dans le contexte d'un Programme de dépistage structuré et fonctionnant bien.

Nous proposons donc pour l'instant de ne **pas prendre de décision de principe en ce qui concerne le dépistage HPV primaire mais de mettre sur pied une période d'étude dans toutes les Communautés, sur un délai d'au moins 5 ans, avec examen approfondi de tous les aspects du dépistage HPV primaire**. Les découvertes récentes ('cancer HPV négatif'), une étude correcte du rapport coûts/bénéfices, les questions de bien-être, la collecte de données belges prospectives, etc. doivent également être prises en compte.

Il est surtout très important d'implémenter un Programme de dépistage du cancer du col de l'utérus structuré et fonctionnant bien dans l'ensemble du pays. Nous sommes disposés à y prêter notre collaboration constructive.

Minister van Sociale Zaken en Volksgezondheid
MAGGIE DE BLOCK

“In your letter, you ask for a 5-year study period. However, there is no reason to wait with the proposed conversion. I do not consider such a study phase to be appropriate. I would like to point out that although the IMC public health decided the transition from a cytological to an HPV-based screening, it first of all indicated that the Sciensano Cancer Center should prepare a plan with all necessary actions and concrete measures to come to such a change. I therefore wish to dispel the perception that this change in the field will be achieved in the very short term”

Current situation

- 25th of march 2019 →roadbook on HPV to be presented to the IMC
  - IMC fiche: "…The focus is mainly on priority actions, including the budgetary implications, the possible tendering procedure, the choice of the test and labs. The renewed screening for cervical cancer should then be able to start on **1 January 2022**"
  - Roadbook lists 14 action points (e.g. selection of HPV tests, definition of laboratory selection criteria…) for which working groups will be installed.
- 22th of may 2019 → IMC follow-up telephone conference
  - HPV Roadbook <u>not</u> accepted (at this moment): **budgetary impact unclear**
  - Ongoing talks with gynecologists, microbiologists, general practioners…

conclusions

- HPV-based screening will replace cytology screening (also in Belgium)
  - Because of scientific debate, a cautious approach is needed
  - A transition period (e.g. Germany/Luxemburg) of co-testing (HPV+cytology) could be advocated- together with the gynecologists
  - Cytology will remain important →should remain an option (free choice) in art. 32
    - <30 years
    - Triage-test ? (p16/KI67 DS? Methylation?)
    - Indication cytology (asked for by gynecologist/general practioner/patiënt)

conclusions

- Timing depends on budgetary impact
  - Independent cost/benefit modelling!!
    - →CPA/GBS already proposed 2 separate –Belgian FR/NL- university studies
    - →Netherlands: initial budget increase (+13% for 5 years, not counting implementation)
    - →january 2022? Not realistic…

Friday 14-6-2019, just another day at work