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The role of HPV in fertility. Should male donor gametes be screened?

In this science-policy advisory report, the Superior Health Council assesses the appropriateness of screening male donor gametes for HPV in the context of assisted reproductive technology in Belgium.

September 2014

1. INTRODUCTION AND ISSUES

The Superior Health Council (SHC) has received a new request for advice from Minister Onkelinx about the role of the human papillomavirus (HPV) in male subfertility and the screening of male donor gametes for HPV. She wishes to obtain the SHC advisory report within 6 months.

HPV is generally known as the infectious agent that causes cervical cancer. However, in recent years it has become clear that infection with this virus can have other consequences as well. Thus, the virus has also been associated with conditions such as anal cancer, head and neck cancers. There is ample evidence that men too carry the HPV, but it is not yet clear what the implications of these findings are. A number of studies carried out on semen show that, though HPV prevalence shows a broad range of variation, clear amounts of this virus can often be found in semen. According to recently published meta-analytic evidence on this subject, semen from subfertile men displays a significantly higher HPV prevalence (16%) compared to that from fertile controls (10%) (Laprise et al., 2014).
In order to meet the Minister's request, an *ad hoc* working group was set up with experts in the field of HPV, gynaecology, *in vitro* fertilisation and reproductive medicine. This working group decided to reformulate the Minister's request into three questions:

These questions are as follows:

- Is there a correlation between HPV-infection and male subfertility? If so, what is the underlying mechanism?

- What are the risks for women who resort to assisted reproductive technology (ART), and indirectly for the unborn child if the donor sperm is HPV-positive?

- Should systematic screening for HPV be considered for male donor gametes (but not when the woman's partner is also the donor)?

2. ADVICE

The SHC provides the following answers to the questions submitted :

- Due to the contradictory outcomes of different studies, it is currently impossible to draw any solid conclusions concerning the causal role of HPV in male subfertility. It also remains unclear what the exact implications of HPV-positive spermatozoa are for the reproductive process.

- It cannot be ruled out that women undergoing intrauterine insemination (IUI) with HPV-positive donor semen are exposed to a certain amount of risk. There is currently no conclusive evidence available on the basis of which this risk could be assessed. It can be considered to be fairly low and certainly not higher than that which the general population is exposed to. In fact, the risk may even be lower, as semen donors belong to a low-risk population for sexually transmitted diseases due to the selection process they are subjected to prior to being accepted by the cell bank.

- Though the risk of HPV being transmitted from mother to child has been described for natural conception, there are only a limited number of cases in which it has actually been proven to have occurred. In addition, even when the child has been infected with HPV from the mother, it is rather uncommon that this should lead to malignancies. In fact, compared to children conceived through normal sexual intercourse, children conceived with clinical assistance may even be at a lesser risk of being infected via the mother. Insemination occurs in a less traumatic way than during natural intercourse, and the semen is collected from a fairly low-risk population.

- Given the current contradictory evidence, it is impossible to carry out a proper assessment of the public health risks involved. However, the number of women seeking ART is fairly low, which means that the implications may be expected to be limited too. There is no agreement over whether or not HPV affects the outcome of the pregnancy. As regards pre-screening donor semen for HPV, the available knowledge does not show that this would have any positive effect on the quality of ART or reduce the risk of HPV-infection in women. Moreover, it could even result in longer waiting lists in the fertility clinics and encourage women seeking ART to explore alternative options that cannot be monitored.

Conclusions

The SHC therefore concludes that the population that resorts to ART is not exposed to a substantially greater risk of contracting HPV than the general population. In fact, their exposure to HPV may actually be lower. Consequently, the SHC is not in favour of screening male donor gametes for HPV. Finally, there is no solid evidence of a correlation between HPV and male subfertility.

Recommendation

The SHC offers to revise its advisory report after two years.

3. FURTHER DETAILS AND ARGUMENTATION

List of abbreviations

ART	Assisted reproductive technology
FISH	Fluorescence *in situ* hybridization
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR HPV	High-risk HPV
ICSI	Intracytoplasmic sperm injection
IUI	Intrauterine insemination
IVF	*In vitro* fertilisation
JO-RRP	Juvenile Onset Recurrent Respiratory Papillomatosis
NK	Natural killer
PAP	Papanikolaou
SHC	Superior Health Council
VLP	Virus-like particles

3.1. Methodology

After analysing the request, the Board and working group Chair identified the necessary areas of expertise. The working group experts provided a general and an *ad hoc* declaration of interests and the Committee on Professional Conduct assessed the potential risk of conflicts of interest.

This advisory report is based on an extensive review of the scientific literature published in scientific journals and in (peer-reviewed) reports from relevant national and international organisations, as well as on the opinion of the experts.

Once the draft advisory report was approved by the working group and by the standing working group "Cells, tissues and organs of human and animal origin", it was ultimately validated by the Board.

3.2. Introduction

3.2.1. HPV

HPVs are very common epitheliotropic viruses that consist of an outer capsid, which in turn encloses a double-stranded DNA genome containing 8000 base pairs. It is likely that over 70% of individuals are infected with at least one HPV strain during their sex life. However, these infections are mostly asymptomatic and clear spontaneously. To date, over 120 HPV genotypes have been fully characterised based on the isolation of complete genomes (de Villiers et al., 2004). About one third specifically infect the anogenital mucosal surfaces. Moreover, high-risk (HR) (carcinogenic) types of these viruses (most notably HPV 16, 18, 31, 33, 35, 45) have emerged as the causative agents of cervical/vaginal/anal (pre)neoplastic lesions. In addition, HPV is also involved in half of vulvar/penile (pre)cancers and in a substantial number of head and neck tumors. As regards low-risk (non-carcinogenic) HPVs, they are associated with benign hyperproliferative epithelial diseases such as warts and condylomata.

In the larynx, a squamous papilloma represents the most common benign tumor in infants and children. These lesions are almost invariably associated with HPV type 6 or 11 and early-onset HPV 11 is more likely to cause a more severe disease (Mounts et al., 1982). The exact mode of HPV transmission in papillomatosis remains unclear. Retrospective and recent prospective studies have suggested that HPV may spread by vertical transmission from mother to child (Tseng et al., 1998). Children born to mothers with active condylomata are at an increased risk of developing papillomatosis (as high as 231 times that of children born to disease-free mothers) (Silverberg et al., 2003). The risk of an infected mother transmitting HPV to her newborn has been estimated between 1:80 and 1:1500 (Shah et al., 1998). Despite this apparent close association, few children exposed to genital warts at birth actually develop clinical disease (Shah et al., 1986). In addition, neonates may become infected before birth, as shown by a recent study according to which approximately 12% of foetuses may develop HPV infections through transplacental transmission (Rombaldi et al., 2008).

At the molecular level, the E6 and E7 viral oncoproteins derived from the carcinogenic HPV induce malignant transformation by interfering with host cell factors that control the cell cycle, apoptosis, cell adhesion, histone acetylation, etc. For example, viral oncoproteins have been shown to complex with p53 and pRB and, as a result, target them for rapid proteasome-mediated degradation. As a consequence, growth arrest and apoptosis are abrogated (Ghittoni et al., 2010). Though carcinogenic HPV infection is a necessary requirement for the development of anogenital (pre)neoplastic lesions, the fact that only a minority of infected men/women actually develop cancer suggests that HPVs are necessary but not sufficient for the development of cancers. Other factors such as immune status, smoking and hormonal factors could also play a significant role in HPV carcinogenesis. A weakened immune system (as observed in human immunodeficiency virus (HIV)-positive patients) is the most frequently mentioned risk factor for HPV infection. Indeed, there is an increasing amount of evidence in support of the fact that there is a strong link between an HIV-positive status and a higher incidence and prevalence of HPV, a reduced likelihood of HPV infection clearance and an increased risk of developing HPV-related (pre)cancers (Herfs et al., 2011).

Even though keratinocytes are the main targets of the HPV and HPVs entering these cells have been shown to cause a productive infection, HPV virus-like particles (VLP) are also able to integrate other cell types, such as immune cells. Though there is no clear tropism of HPV to white blood cells, some authors reported HPV-DNA associated with circulating leukocytes in human and animal models and in healthy blood donors (Kay et al., 2005; Chen et al., 2009). *In vitro* experiments demonstrated the incorporation of HPV VLP in dendritic or Langerhans cells (Herman et al., 2010; Bousarghin et al., 2005). Moreover, there is also recent evidence in support of the hypothesis that natural killer (NK) cells and lymphocytes B are possible targets of the HPV (Renoux et al., 2011; Reijmers et al., 2013). Interestingly, Foresta et al. detected the viral E6 protein together with HPV DNA in NK and B cells present in semen, suggesting that HPV infection could be productive (Foresta et al., 2013).

3.2.2. Assisted reproduction

Assisted reproduction treatments have been available for over 50 years.
Different techniques are used to help infertile patients, including IUI and *in vitro* fertilisation (IVF), with or without intracytoplasmic sperm injection (ICSI).

- Intrauterine insemination is a simple technique in which a small amount (250 µl) of a suspension of processed spermatozoa is injected inside the uterus through a soft plastic catheter at the time of ovulation.
- *In vitro* fertilisation is a technique in which the oocytes are collected from the ovaries and cultured with 2500 to 5000 processed sperm cells for fertilisation. In case of severe male infertility, the oocytes are fertilised by injecting one processed sperm cell inside the oocyte's cytoplasm.

Sperm of the male partner is commonly obtained through masturbation or sometimes with the use of a special condom during intercourse. The fresh semen is then directly processed for insemination. Semen processing involves first washing the semen sample by centrifugation to remove the seminal fluid, epithelial cells, germs, cytokines, white-blood cells if present and to achieve a concentrated motile spermatozoa sample. All manipulations of the semen sample are performed under sterile conditions to avoid germ contamination.
Prior to accepting patients for ART treatment, fertility clinics collect information on the couples to assess the indication for treatment and to screen them for the most common viral infections or sexually transmitted diseases, including hepatitis B virus (HBV), hepatitis C virus (HCV), HIV, syphilis (as specified in the Belgian Law of 19 December 2008).

In 2013, sperm banks registered approximately 250 new donors in Belgium (Thijssen et al., 2014). In the past, sperm donors were recruited among a high-risk student population, but nowadays, the sperm-donor pool has shifted, with donors being increasingly selected among a lower-risk non-student population.

The sperm provided by sperm banks is collected from male donors who visit the bank. The sperm is then mixed with cryopreservation solutions to be stored in plastic straws in liquid nitrogen. The sperm can be frozen either as it is or after processing. Sperm donors are screened for frequent genetic diseases such as cystic fibrosis, sickle cell anaemia, thalassemia, abnormal karyotype and most importantly, for sexually transmitted diseases (HBV, HVC, HIV, syphilis). The semen parameters must be above the normal range (sperm count, sperm motility, normal forms) for a donor to be accepted.
However, neither the recipient couples, nor the male gamete donors are specifically tested for HPV. In fact, no such screening is recommended, with HPV usually transmitted through sexual activity, which is something couples usually engage in.

This in turn means that HPV contamination may occur at any moment during the couple's life.
Still, the use of a semen donor may increase the risk of a woman contracting HPV through IUI. Yet this observation is more relevant for homosexual couples or single women.

Screening women for HPV: in Belgium, it is recommended to carry out HPV screening only in the event of the Papanikolaou (PAP) smear revealing the presence of cervical lesions or cell anomalies and in the follow-up of high-grade intra-epithelial lesions. It follows that there is

currently no information available about the HPV status of the woman at the time of the insemination.

3.2.3. Correlation between HPV and fertility

3.2.3.1. HPV and early embryo development

In vitro studies on early embryo development have pointed out that infection with HPV 16 or 18 may impair embryo development. In these studies, the oocytes or the embryos were directly exposed to a fragment of the HPV genome. In mice, the DNA of infected blastocysts was significantly more fragmented than that in controls (Calinisan et al., 2002). Blastocysts displayed a higher level of apoptosis. The study suggests that blastocysts exposed to 0.01 µg DNA/µL HPV 16 fragments can be affected by HPV viral particles. However the number of blastocysts analysed was too small to calculate the incidence. A previous study had already shown that HPV-16 and 18 from the sperm was found in the inner cell mass and trophectoderm cells (Cabrera et al., 1997). Later work, which was also performed on mouse embryos, showed that HPV infection in early embryos can inhibit the cleavage of 2-cell embryos and blastocyst hatching (Henneberg et al., 2006).

All these studies were performed *in vitro* on mouse embryos, which were directly exposed to HPV DNA fragments. In fact, this is a situation that is very different from that which prevails *in vivo*.

3.2.3.2. HPV and miscarriage

HPV DNA was shown to colonise trophoblastic cells *in vitro* and it has been claimed that there is a causal link between HPV-infection and miscarriages (Liu et al., 2001; You et al., 2008). However, this is controversial. Two clinical studies observed a higher percentage of HPV DNA in spontaneous miscarriage samples, whereas three subsequent studies involving larger patient cohorts, did not find any such correlation between HPV and early spontaneous abortion (Skoczynski et al., 2011; Conde-Ferraez et al., 2013; Ticconi et al., 2013; review by Noventa et al., 2014).
Approximately 15% to 24% of women with a full-term delivery tested positive for HPV-DNA, compared to 17.7% to 24.4% of women who suffered a spontaneous miscarriage (Skoczynski et al., 2011).

3.2.3.3. HPV and semen donors (non-partner donor)

Kaspersen et al. (2011) analysed the prevalence of HPV in 267 semen samples from 188 semen donors. They included 74 semen donors undergoing the selection process and 114 samples from active semen donors. For some donors, multiple ejaculates were tested. The overall prevalence was 16%, but turned out to be no more than 2.1% for HVP 16. HPVs bind mainly at the equatorial region of the spermatozoa. FISH analysis (fluorescence *in situ* hybridization) also revealed that in positive ejaculates, only between 1% and 16.5% of the spermatozoa were actually positive themselves. Yet the main serotypes were 16, 51, 52, 31, 53. Though data on HPV prevalence from Belgian donors are scarce, D'Hauwers et al. (2012) reported positive cases among a limited series of samples. Of the 82 samples tested using a sensitive real-time PCR assay, only 2 were positive for HR HPV (2.4%). After genotyping, both samples were found to be HPV 39. Due to the

limited sample size, these figures need to be approached with due caution, and further evaluation is essential. Not only the presence of HR HPV DNA needs to be considered, but also the genotypes found. Although 15 HPV genotypes are considered to be oncogenic, not all of them display the same virulence. There is also an important discrepancy between the HPV genotypes detected in the general population versus the HPV genotypes that are actually found in carcinoma. HPV 16 and HPV 18 are the most prevalent types in cancerous lesions, whereas HPV 39 occurs to a much lesser extent.

3.2.3.4. Risk of HPV transmission through ART

Semen donors are healthy men selected among a population at a low risk of sexually transmitted disease. Data on a small sample of semen donors showed that the proportion of donors with HPV-positive semen can be as high as 16%, but only 2.1% of these were positive for HPV 16. Inter-sample variation has been observed for individual donors with respect to the presence of HPV.
Data suggest that HPV can be present on spermatozoa and could be a vector for HPV transmission. The proportion of HPV-positive sperm cells is very low. For ART, the semen is washed (processed) before use. In ART, this further reduces the risk of HPV transmission.

3.3. Correlation between HPV-infection and subfertility in males

There are reports according to which HPV has been found in semen (Rintala et al., 2004). Different authors have hypothesised that HPV can modify spermatic parameters, causing a reduction in sperm motility, alterations in the seminal pH and spermatozoa DNA fragmentation (Foresta et al; 2010; Connelly et al., 2001; Lee et al., 2002). Although *in vitro* studies demonstrated that spermatozoa are able to carry HPV DNA and to transfer it to oocytes, it is still not clear whether the HPV-infected sperm is able to fertilise oocytes *in vivo* and to transfer the viral genome (Foresta et al., 2011). These uncertainties extend to the subsequent steps of conception because it is not clear whether the infected oocytes are able to generate normal embryos and whether the infection itself can interfere with implantation and the subsequent progress of the pregnancy (Garolla et al., 2012).

The relationship between HPV-infection in men and abnormal sperm quality is controversial. Most data have been obtained by *in vitro* studies and more studies are required to define the role of HPV-infected sperm in clinical practice (Gizzo et al., 2014). There are reports according to which there is no significant correlation between seminal HPV DNA infection and abnormal sperm parameters (Didelot-Rousseau et al., 2007; Golob et al., 2014).

The recent publication by Laprisse et al. (2014) summarises the information obtained from 27 studies, and is, to the best of our knowledge, the most comprehensive study conducted so far regarding the relationship between HPV-infection and male infertility. The authors recognise the lack of conclusive evidence in support of a link between male infertility and an HPV-positive status. Other sources have strongly suggested that HPV plays a part in male subfertility (Garolla et al., 2012), as well as that there is a correlation between an HPV-positive status and spontaneous miscarriages.

A wide range of HPV DNA prevalence data can be found in different reports (1.3% - 72.9%) (Giuliano et al., 2010), and studies indicate that the clearing rate is higher in men than it is in women (median clearing time is 6 months). The publication by Laprisse et al. failed to draw a distinction between HR HPV and other, less harmful, HPV types. Including all HPV genotypes in the meta analysis could lead to higher overall HPV prevalence data, but would not necessarily indicate an increased risk for disease. The meta analysis suffers from a high degree of heterogeneity, mainly due to the different HPV detection methods used in the original publications. The outcomes can be highly dependent on the sensitivity of the test used, as well as on the range of HPV types detected. When limiting the data to recent reports on HR HPV only, a more limited range of HPV DNA prevalence can be found (1.3% - 15.4%).

Conclusion:
Due to the contradictory outcomes of different studies, it is currently impossible to draw any solid conclusions concerning the causal role of HPV in male subfertility. It also remains unclear what the exact implications of HPV-positive spermatozoa are for cell biology.

3.4. Risk for the woman

As discussed above, most women (> 70%) contract an HPV-infection during the course of their sex lives, making HPV one of the most common sexually transmitted infections (Zimet et al., 2009). In an estimated 90% of the cases, the natural immune response is able to clear the infection without inducing significant cervical abnormalities. It has been recognised that sexual intercourse is a much more efficient route of infection than IUI (Laprise et al., 2014). Indeed, most infections with HPV will occur at the transition zone between the columnar endocervical epithelium and the squamous exocervical epithelium. It is believed that microtrauma induced by sexual activity enhance the chances of infection of the basal layer of the squamous epithelium. Catheters used for IUI are designed to negociate the cervix easily but also to minimise any potential trauma to the endocervix and endometrium (van der Poel N et al., 2010).
Intrauterine insemination is thus less prone to the induction of microtrauma at the transition zone.

Some infections will not remain transient, but will evolve into a persistent infection. Persistent infection with a HR HPV type is generally accepted to be the necessary cause for cervical cancer development. Not all HR HPV types display the same virulence, and infections with HPV 16/HPV 18 are known to be most potent in transforming epithelial cells into cancer cells. Together, they are responsible for 70% of all cervical cancer cases. The prevalence of HPV 16 in the Belgian female population is believed to be 3.7% and that of HPV 18 around 1.5% (Arbyn et al., 2009). Kaspersen et al. found a high prevalence of HPV 51 and HPV 52 in donor semen, and a lower prevalence of HPV 16 (2.1 %) and HPV 18 (1.1 %).

Conclusion:
Given the information above, it cannot be ruled out that women undergoing IUI with HPV-positive donor semen are exposed to a certain amount of risk. Yet the figures above and the design and use of catheters for IUI suggest that this risk can be considered fairly low. There is currently no conclusive evidence available on the basis of which this risk could be assessed.

3.5. Risk for the child

Merckx et al (2010) conducted a meta-analysis that draws the following conclusion: children born to HPV-positive mothers are more liable to be HPV-positive themselves. This meta-analysis was unable to prove the existence of a causal link, nor was it able to determine whether the transmission is mainly antenatal/ perinatal or whether it occurs after the delivery. Syrjänen (2010) describes different types of potential mother-to-child transmission, viz. periconceptual, prenatal, perinatal transmission, as well as horizontal transmission and autoinoculation. A range of HPV-related conditions in children has been described, including oral papillomas, Juvenile Onset Recurrent Respiratory Papillomatosis (JO-RRP), and (ano)genital warts (non-sexually transmitted) (Syrjänen et al., 2010), all of which have a rather low prevalence. HPV-infections in underage children are commonly asymptomatic. In contrast to these findings, recent findings by Koskimaa et al. (2014) suggest that HPV-infections in children born to HPV-positive mothers actually have a protective role, with these children displaying greater HPV-specific immunity.
Mother-to-child transmission of HR HPV has gained more attention in the recent past, and evidence for the existence of this phenomenon is accumulating. However, this does not result in a high prevalence of HPV-related morbidity in children. It is entirely unclear what the long-term effects of such early infections can be (e.g. latent infection in the newborn that would predispose the child to developing HPV-related diseases in adulthood).

Conclusion:
Though the risk of the HPV-infection being transmitted from mother-to-child has been described for natural conception, there are only a limited number of cases in which it has actually been proven to have occurred. In addition, even when the child has been infected with HPV from the mother, it is rather uncommon that this should result in malignancies. In fact, compared to children conceived through normal sexual intercourse, those conceived with clinical assistance could even be at a lesser risk of being infected via the mother. Insemination occurs in a less traumatic way, and the semen is collected from a rather low-risk population.

3.6. Public health risk

Sexual activity is the main cause of infection with HR HPV, and most women are infected with the virus during their lives, whilst only a limited number of women develop persistent infections. From a public health point of view, the IUI of HPV-positive semen could indeed induce an infection with HPV, though this is less likely to occur than it is during normal sexual intercourse. Therefore, it cannot be ruled out that women undergoing IUI with HPV-positive donor semen are exposed to a certain amount of risk. There is currently no conclusive evidence available on the basis of which this risk could be assessed. It can be considered to be fairly low and certainly not higher than that which the general population is exposed to. Laprisse et al. suggest that the issue of HPV-infection and the potential risks involved should be included in the information provided to women seeking IUI (Laprisse et al., 2014). A direct consequence of testing donor semen for HPV would be that an estimated 10% of the samples would turn out to be positive for HR HPV, and would therefore need to be discarded (Kaspersen et al., 2011; D'Hauwers et al., 2012). Given the growing demand for donor semen and the shortage of donors, this could have significant implications for fertility clinics. Yet more important are the implications for public health in general: in many countries facing a shortage of donor sperm, recipients on waiting lists are increasingly recruiting

so-called "wild-donors", thus creating a parallel grey circuit with (potentially high-risk) donors, which in turn gives rise to uncontrollable health risks.

Furthermore, some reports mention a higher rate of spontaneous abortions or premature deliveries in HPV-positive couples. These findings are not consistent with other reports, and are still a matter of ongoing debate (Dana et al., 2009). If these findings should be confirmed, this would also result in additional health requirements at the level of the Obstetrics and Gynecology departments.

Some authors (including Kaspersen et al., 2011; Noventa et al., 2014) suggest primary HPV prevention as a potential avenue to explore. It could be worthwhile to give priority to couples (both partners) under ART in receiving (opportunistic) prophylactic HPV vaccination prior to semen injection. The current vaccines provide protection against the two major high-risk HPV types (HPV 16 and HPV 18), and the quadrivalent vaccine offers additional protection against the two most prevalent low-risk types (HPV 6 and HPV 11).

Conclusion:
Given the current contradictory evidence, it is impossible to carry out a proper assessment of the public health risk. However, the number of women seeking ART is fairly low, which means that the implications may be expected to be limited too. There is no agreement over whether or not HPV affects the outcome of the pregnancy. Pre-screening donor semen for HPV could even result in longer waiting lists in the fertility clinics and encourage women seeking ART to explore alternative options that cannot be monitored.

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5. COMPOSITION OF THE WORKING GROUP

All experts joined the working group ***in a private capacity***. The names of the experts appointed by Royal Decree as well as members of the Committee and the Board are available on our website (web page: composition et fonctionnement). The general declarations of interests of the experts who approved or validated the advisory report are available on our website (web page: Conflits d'intérêts).

The following experts were involved in drawing up the advisory report :

DE SUTTER Petra	Gynaecology, reproductive medicine	UZGent
DELVENNE Philippe	Anatomopathology; human papillomavirus	ULg
DEVREKER Fabienne	Gynaecology, reproductive medicine	ULB
SWENNEN Béatrice	Epidemiology, vaccinologie	ESP-ULB
TOURNAYE Herman	Gynaecology, reproductive medicine	UZBrussel
VAN DEN ABBEEL Etienne	Embryology	UZGent
VANDEN BROECK Davy	Virologie	UGent

The working group was chaired by Etienne VAN DEN ABBEEL, the scientific secretary was Muriel BALTES.

The administration was represented by:

HUE Didier	Clinical evaluator	FAMPH

The following experts read and approved the advisory report:

BAUDOUX Etienne	Medicine, cell therapy	ULg
BEELE Hilde	Medicine, dermatology	UZ Gent
GUNS Johan	Medical-social sciences	UZ Brussel
HEINEN Ernst	Histologie humaine	ULg
MUYLLE Ludo	Medicine, clinical biology	FAMHP, UZA, UA
PIRNAY Jean-Paul	Medical sciences	MHKA
THONON Fabienne	Reproductive medicine, embryology	CHR de la Citadelle de Liège

The working group was chaired by Hilde BEELE, the scientific secretary was Muriel BALTES.

About the Superior Health Council (SHC)

The Superior Health Council is a federal body that is part of the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC takes no decisions on the policies to follow, nor does it implement them. It does, however, aim at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, members of scientific institutions), 200 of whom are appointed experts of the Council. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a referring committee) and 4) the final endorsement of the advisory reports by the Board (ultimate decision-making body). This coherent set of procedures aims at allowing the SHC to issue advisory reports based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

The advisory reports drawn up by the working groups are submitted to the Board. Once they have been endorsed, they are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.shc-belgium.be), except as regards confidential advisory reports. Some of them are also communicated to the press and to target groups among healthcare professionals.

The SHC is also an active partner in developing the EuSANH network (European Science Advisory Network for Health), which aims at drawing up advisory reports at the European level.

In order to receive notification about the activities and publications of the SHC, you can send a mail to info.hgr-css@health.belgium.be .