A Conversation with Dr. Xavier Bosch, winner of the 2021 Hilleman Award

Dr. Francesc Xavier Bosch Jose (MD, MPH, PhD, DHC) is an eminent epidemiologist whose scientific career has focused on the research of cancers associated to infectious agents, notably on cancer of the liver, the cervix, the genital tract and of the oral cavity and oropharynx. Dr. Bosch worked as epidemiologist in the International Agency for Research on Cancer (IARC, 1982-1993) and as Visiting Scientist in the National Cancer Institute (NCI, 2002). He served as Director of the Cancer Epidemiology Research Program on the Catalan Institute of Oncology (ICO, 1994-2015), and has collaborated with several public health agencies and scientific organizations such as the Pan American Health Organization (PAHO), the World Health Organization (WHO) or the European Research Organization on Genital Infection and Neoplasia (EUROGIN) among others.

Dr. Bosch's research at IARC was instrumental in demonstrating the causal role of Human Papilloma Virus (HPV) in cervical cancer, establishing the role of the environmental co-factors for carcinogenesis among HPV-positive women, and describing the international variation of HPV types in cervical cancer and some of its major variants. His studies triggered both the first HPV vaccine clinical trials and the evaluation of HPV tests as screening tools.

Today we proudly acknowledge Dr. Bosch as the recipient of the 2021 Maurice Hilleman Award. IPVS had the recent pleasure to speak with Dr. Bosch and capture some highlights from his journey toward proving the connection between HPV and cervical cancer.

Dr. Bosch, you tried to bid farewell to the HPV community with a very nice personal note at the closing ceremony of IPVC 2020. But it looks as if we found a way to keep you around a bit longer.

1. ***What was your first reaction to the news of receiving the 2021 Hilleman award?***

   It was quite unexpected. As an oncological researcher focused on proving the connection between HPV and cervical cancer, I never expected to be associated with the tremendous vaccinology legacy of Maurice Hilleman. It's only in the 'last laps' of my career that vaccines have become central to my work. It is of course an honor.

2. ***What led you to suspect the connection between HPV and cervical cancer?***

   I was one of many researchers pursuing this connection from different angles at more or less the same time. Like the saying, 'wherever it begins, all water ends up in the Amazon River'.

   Or 'many roads lead to Rome'?

   Exactly. Colleagues from other disciplines were travelling different routes to arrive at the same causality conclusion. I guess our group was one of the first to get there from the path we followed.

   Tell us about the path.

   In the late 1980s, together with Dr Nubia Muñoz and my colleagues at IARC, in Spain and in Colombia, we set up a case control study to investigate the role of men in transmitting *the risk* of cervical cancer to women. As we were preparing the protocols, we came across a presentation from the German group of Professors Zur Hausen and Lutz Guissman in Heidelberg. It suggested that while not clinically apparent, HPV could be the long-term sexually transmissible agent that could be at the origin of the cell transformation that leads to cancer. So before starting with our fieldwork, we added the necessary protocols to collect biological specimens. The specimens had to be stored for quite some time while consensus was reached on how best to evaluate them for traces of viral DNA.

Undoubtedly, the development of DNA technology significantly accelerated this research. We were able to move from a simple risk analysis searching to correlate the number of sexual partners a woman may have had in her life with the risk of developing cervical cancer; to being able to study a person's cells to find viral DNA, making the analysis much more precise and findings more concrete. This was a big step forward for molecular epidemiology.

3. ***Was the theory that HPV can cause cancer met with much skepticism?***

Perhaps some, but don't forget that HPV is the third virus proven to cause human cancer. Hepatitis B and C were the first viruses proven to cause LIVER cancer (and chronic liver disease). Maurice Hilleman developed one of the first vaccines against hepatitis B. So there was a human precedent.

4. ***How did it occur that you and your colleagues were able to provide the first clear evidence that infection with specific HPV types was the major risk factor for the subsequent development of cervical cancer in women?***

It was long suspected that there was a sexually transmitted factor involved in developing cervical cancer. Many researchers had spent decades looking at Herpes Simplex type 2 as a possible culprit, but findings were frustratingly inconsistent. HPV was suggested as a possible alternative by Prof. Zur Hausen, who received the Nobel Prize in 2008 for his research. The HPV community celebrated this recognition as a collective triumph. In the early 1990s, we had different diagnostic technologies to use in epidemiological studies, but proper validation was still lacking. We analyzed the entire collection of specimens from two case control studies in Colombia and Spain, using three of the most promising technologies: Southern blot, Dot blot, and an early version of the PCR. Our first publication about this project in 1992 revealed that the link between HPV and cancer was indeed uniquely strong. As the sensitivity of the technology increased, the strength of association also increased. The research was extensive, thorough and delivered highly consistent evidence of causality. It caused a stir that the results were coherent with other epidemiological studies (cohort, prevalence and natural history studies), as well as with animal experiments and molecular investigations. The picture became much clearer. Researchers invested a great deal of effort to characterize the association and prove the consistency of the findings internationally. Naturally, the results sparked the exploration of possible preventative alternatives.

5. ***How did it feel to be able to deliver this evidence? Did you have a 'Wow! We found it!' moment? Did the team head for the nearest bar to drink a glass of champagne?***

I was working late on a Friday evening at IARC in Lyon when I received a phone call from virologist Dr. Keerti Shah in Baltimore. He was in charge of analyzing the specimens. Dr. Shah shared some preliminary HPV DNA test results from a few hundred specimens from cases and controls. I jotted down some key figures on the back of an envelope, and after a quick calculation we realized, **THIS IS IT!** The association between HPV exposure and cervical cancer (and later on shown for other cancers) was extraordinarily high compared to the typical risk estimates findings in cancer epidemiology. We were awestruck by the magnitude of the proof we held in our hands. That night it became clear that most of our work in coming years would deal with these astonishing results and their consequences.

Champagne time?

Not that evening, but of course we found the time to toast this astonishing result of the whole team!

What happened next?

Those results went back in the drawer while we scrutinized the findings from every angle available. The next several months were spent meeting with groups of scientists and review boards to present and discuss the findings.

Another **'wow moment'** came a few months later, during a cold winter workshop at the University of Brussels, organized by Dr. Nubia Munoz of the IARC. After three long days of consultation in a dank, gloomy university facility, the late Dr. Shah turned to the audience and softly said, "**Causality has been proven beyond a reasonable doubt**". That was a profound moment I shall always remember.

It was time to communicate the connection between HPV and cervical cancer to the world. Even after all the reports and discussion with peers, this was daunting. Causality is a powerful word, and in this case, we claimed that HPV was not only "a cause" but "the necessary cause". This means that essentially, all cervical cancer cases are caused by HPV and therefore, in the absence of HPV there should not be cervical cancer. Still with a bit of trepidation, we determined to include the word 'causal', in the title of the 1992 paper reporting on the Colombia and Spain study. But it was the last sentence that was most exciting; it indicated that **because the culprit is a virus, there is opportunity to create an effective vaccine and prevent cancer through vaccination**.

The team didn't stop there. We continued to publish additional articles in the scientific literature and monographs in the IARC'S scientific publication series to demonstrate that the causality claim between HPV and cervical cancer was irrefutable. We also clarified earlier findings on the roles of the other risk factors typically associated with cervical cancer, such as the lifetime number of sexual partners a woman may have had, her age when she started having sexual intercourse, smoking, OCs, parity, other STIs, etc. And we confirmed the findings internationally in a set of studies that examined specimens for over 23,000 cancer cases worldwide.

All scientific precautions were taken before calling a full IARC monograph review in 1995 that established HPV as a "group A" human carcinogen. We had to overcome the fear that we might somehow make an erroneous claim, which is of course a researcher's worst nightmare. The HPV monograph program involved about 100 experts evaluating the literature and preparing working documents that were reviewed word-by-word in plenary sessions. At the end of that phase, the group produced a book with unambiguous conclusions on the carcinogenic potential of the human papillomavirus.

6. ***You also delivered another causality paper to the American FDA in 2001. Why was that necessary?***

Claiming cancer causality had enormous ramifications. The paper in 2001 became a landmark moment for cervical cancer screening. The FDA was looking at the first assay that was proposed for screening for HPV. It was a big change in approach to go from looking at cells (pap smear) to testing for a virus.
The evidence of HPV causality could potentially modify what had been the standard screening practice over the last 50 years. Cytopathology labs were being asked to change their routines. There were significant commercial implications. So there was push-back toward the claim that HPV can cause cervical cancer.

When the first clinical test (Hybrid Capture 2) was presented to the FDA for licensing, it was turned down at the first review because "causality had not been proven". I was then commissioned to write an academic position paper on the causality connection. Once that paper was added to the dossier, the objections about insufficient evidence subsided and the conclusions started to be widely accepted. The HPV screening proposal became the reference, and most guidelines today include HPV testing as part of the basic algorithm. A few years later, in 2006, the HPV vaccine became available to the general population further reshaping the screening proposals for vaccinated young women.

7. ***One reason you've received the 2021 Hilleman Award is your tireless work to promote and facilitate the implementation of HPV vaccination all over the world, with dramatic positive global impact on women's health. Since 2002 when the first HPV vaccine trial was reported by Dr. Koutsky et al, over 120 million women have been vaccinated against HPV. What's your approach to promoting the HPV vaccine?***

There is a chain of influence that begins with professional education of health care providers (HCPs) embracing various professionals. They are not HPV specialists, but they interface with the general population, advising families on issues like participating in screening and vaccination programs. The HPV professional community has a responsibility to keep generating and spreading knowledge to HCPs in clear, simple terms that they can then use to inform and advise their patients.

It has been and still is a tremendous communication challenge. Amongst other, we were asking that

- the full population of an eligible age and gender be vaccinated against HPV
- screening be done in a different way than before
- Deal with the stigmas and taboos of a sexually transmitted disease if found HPV positive either at screening or clinically.
- understand how to avoid transmission to others

Introducing a new vaccine and a novel screening technology for HPV cancer prevention requires the acknowledgement and endorsement of many types of health professionals and of the health care systems in operation. The level of understanding and most certainly the opinion of GP's, pediatricians, nurses, midwives, vaccinologists, gynecologists…are critical to how they inform their patients. It takes an enormous ongoing communication effort to build and maintain a level of informed consensus that influences healthcare providers, the public, the views of public health authorities and health economists. New messages must be repeated time and again in order to build confidence in them.

8. ***We see healthcare education changing. Are we making progress?***

Yes. Education of healthcare professionals is changing in exciting ways. In the past, proximity to major cities was correlated to the quality of healthcare available. Face-to-face instruction has limitations that are largely removed in the on-line learning environment. E-learning helps level the playing field by offering the same high-quality level of instruction to professionals at all hospitals no matter how remotely situated or modest their facilities may be.

E-learning really got a boost from the COVID pandemic. When we started building the e-oncologia educational program in Barcelona, it was something of a novelty. Now it seems everyone is trying to offer more on-line instruction. The e-oncologia program currently offers 2,500 hours of oncological training delivered by the best specialists in Spain. It also has several courses on HPV and cancer prevention in 7 languages that expand through interested channels. It is really nice to come to work on a Monday morning and see that a new group of students has formed around a tutor somewhere in the world and has started using our course materials. No fees, no rewards, little bureaucracy…just interest in learning and sharing the information. A spin-off benefit is that the students may form an on-line network from those who have studied together to continue the learning process. Our group animated the edition of a series of 13 HPV monographs (Vaccine journal special issues) reporting on the epidemiology and prevention of HPV and cancer in the 5 continents and we are also publishing a weekly e-newsletter called HPV World, distilling evidence-based HPV messages and relevant updates for clinicians in reader-friendly e-formats.

9. ***Do you think that educating HCPs is an effective way to tackle vaccine hesitancy?***

Yes, but not exclusively. Social education will also play a critical role in the coming years. The anti-vax movement is becoming increasingly politicized, to the point where we witness violent clashes in the streets in many developed countries that raise the antivax flag in their struggle against governments. The COVID pandemic has pitted individual freedom against science. Some political groups assert that governments that impose public health recommendations like vaccines on society are infringing on the right to self-determination. The WHO has identified addressing anti-vax sentiment and vaccine hesitancy as one of the top 10 priorities in health for the decade.

10. ***What do you consider to be the greatest obstacle in training HCPs about the tools we have to beat HPV and prevent HPV cancer?***

Shortage of educational funding and expertise. We need to structurally address the proper interaction between science and industry. We should reflect on lessons learned from the COVID pandemic. How can educational initiatives more easily source funds from industry without exposing the scientist/instructor to allegations of compromised objectivity? We need to support structural and transparent approaches to address this problem so that more funding and activity can be made available. Some such structures already exist and are working well.

11. ***Do you have a final message for us as you accept this award?***

I wish to reiterate my gratitude to the professional field and to the International Papillomavirus Society for the 2021 Hilleman Award, which I accept on behalf of my team. We live in unexpected times, where an infectious disease pandemic has challenged the running of the world's economy and the daily life in many countries. We are quickly learning how to overcome the challenges, which should illuminate the way towards better prevention measures. Preventing cancer by vaccination and better screening is now a realistic possibility in many developed countries and a window of hope for the world. It is also a triumph in healthcare. We should take these lessons to heart and move forward.

November 2021 *Interviewed by C. Amsinger, IPVS*