

# VIRUSES AND VACCINES

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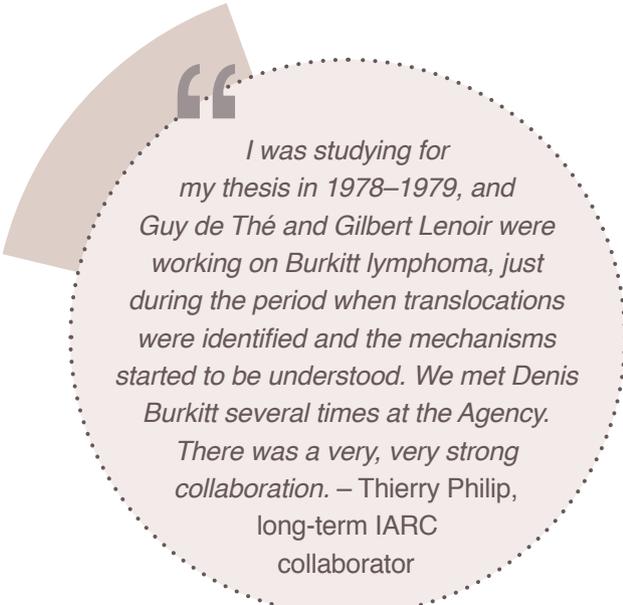
Which cancers in humans are caused by a virus? In the late 1950s, asking this question was fully justified, given the evidence on cancers induced by viruses in several animal species. The first evidence came from Peyton Rous's pioneering experiments with sarcoma in chickens in 1910 (recognized with the Nobel Prize 56 years later). Since the 1930s, results had followed in rabbits, mice, frogs, ducklings, turkeys, and guinea fowl. Among other findings, these studies showed the possibility of transmission of carcinogenic viruses between species. The first answer to the question of virus-induced cancers in humans came from Africa.

## BURKITT LYMPHOMA

The first report of the malignancy that became known as Burkitt lymphoma was published in 1958 (see "The discovery of Burkitt lymphoma in East Africa"). The search for possible causes soon began, and led in 1964 to the identification of a new virus of the herpes family, named Epstein-Barr virus (EBV) after its discoverers. EBV is a DNA virus with versatile properties: it was found to silently infect people from an early age in most countries; it turned out to be the agent of infectious mononucleosis, which is most common among adolescents and young adults; and in the laboratory it became a tool for "immortalizing" lymphoid cell lines, making them continue to grow indefinitely. IARC participated in research on Burkitt lymphoma from its earliest days. It contributed to the standardization of methods to measure anti-EBV antibodies and directed serological surveys to detect the presence of EBV in East Africa. In 1972, IARC initiated a

large-scale prospective study in five counties of the West Nile District of Uganda (see "IARC's prospective study in the West Nile District of Uganda").

The title of the second volume of the IARC Scientific Publications series, *Oncogenesis and Herpesviruses*, published in 1972, documents IARC's interest in the wider field of cancer and herpesviruses. The possibility that these agents, and in particular EBV, could be involved in the development of cancers other than Burkitt lymphoma was suggested by findings of elevated concentrations of anti-EBV antibodies in cases of nasopharyngeal cancer, a tumour frequent in populations of Chinese origin.



*I was studying for my thesis in 1978–1979, and Guy de Thé and Gilbert Lenoir were working on Burkitt lymphoma, just during the period when translocations were identified and the mechanisms started to be understood. We met Denis Burkitt several times at the Agency. There was a very, very strong collaboration. – Thierry Philip, long-term IARC collaborator*

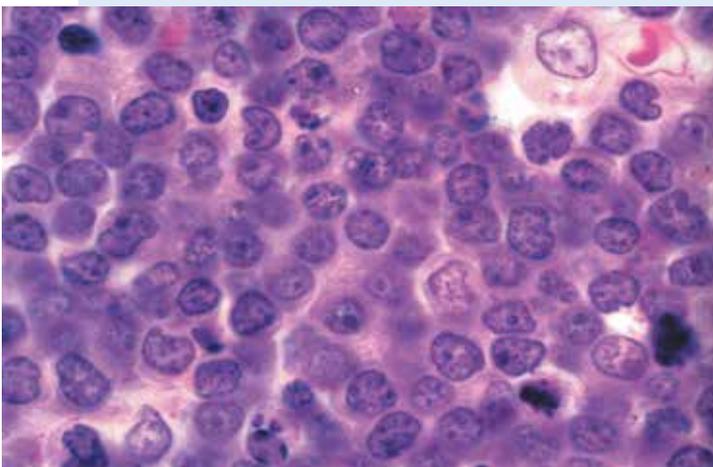
## THE DISCOVERY OF BURKITT LYMPHOMA IN EAST AFRICA

It had long been known, since the arrival of the first missionary doctors, that various childhood tumours were especially frequent in tropical Africa. Denis Burkitt, an Irish “bush surgeon” practising in Uganda, reasoned that “there is an obvious difference between describing the features of individual trees and recognizing the configuration of the wood, which is composed of the sum total of many trees growing in relation to one another.” He thus realized that “a number of tumours occurring in children in different anatomical sites tended to be related to one another in individual patients. The simultaneous occurrence of tumours in different locations such as the maxilla, mandible, thyroid, ovaries, liver and kidneys demanded explanation and suggested a common origin. The clinical distribution appeared to preclude a primary tumour with bizarre metastases, and the alternative of a multifocal tumour seemed to be more acceptable.”

Soon after the clinical identification, there was histological confirmation that the different tumours were all part of a single neoplastic condition, a malignant lymphoma that arises in lymphoid B cells. The newly described cancer was named after Burkitt. Cases were then documented in other parts of Africa. Today it is known that Burkitt lymphoma occurs in three contexts: in equatorial Africa, where it is the most common childhood malignancy; throughout all other parts of the world, where it is a rare tumour; and in association with HIV/AIDS.



*Denis Burkitt (left) with former IARC staff member Gregory O'Connor (centre) and pathologist Dennis Wright at a reception during an IARC meeting on Burkitt lymphoma.*



*Typical histological appearance of Burkitt lymphoma. The tumour cells are uniform in size and shape, intensely coloured upon staining, and accompanied by occasional “starry sky” patterns (upper right) of benign large cells that have ingested fragments of dead tumour cells.*

## IARC'S PROSPECTIVE STUDY IN THE WEST NILE DISTRICT OF UGANDA

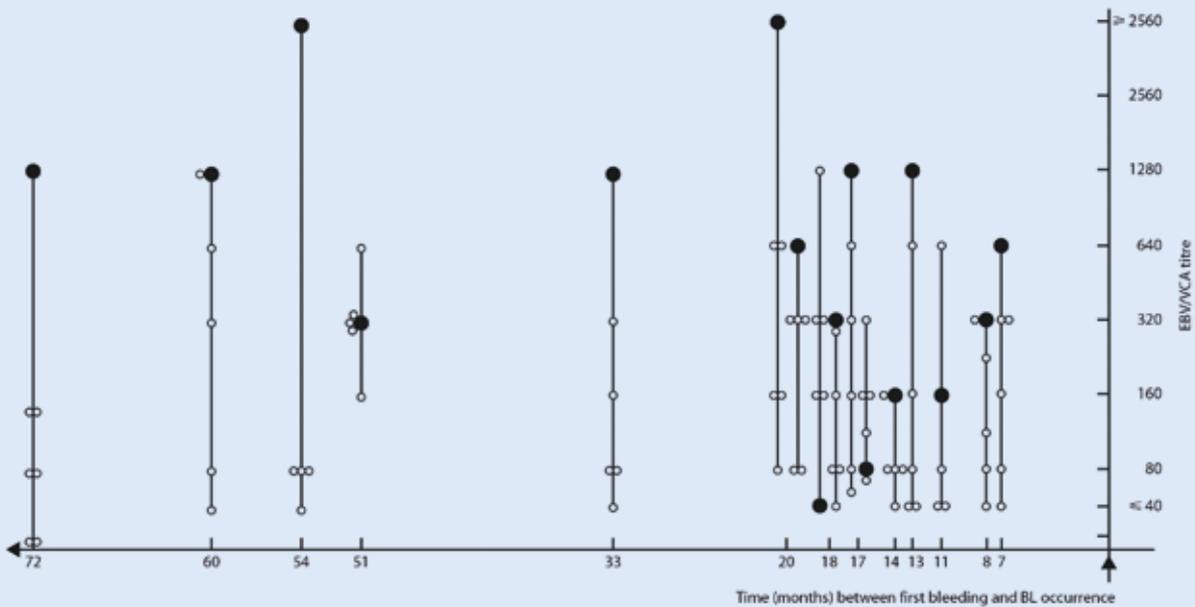
This prospective study was directed in the field by IARC scientists Guy de Thé and Anton Geser. From 1972 to 1974, about 42 000 samples of blood serum were collected from children aged 0–8 years living in five selected counties of the West Nile District of Uganda. In 1979, civil disturbances made it unfeasible to continue with case finding to identify Burkitt lymphoma cases among these children. By then, 16 cases had been recorded.

The serum samples of each case were tested for infection with Epstein–Barr virus (EBV), as evidenced by the concentration of anti-EBV antibodies, along with the serum samples of five control children of the same

age and sex who had not developed Burkitt lymphoma during the years of follow-up. In most comparisons, the antibody concentrations were found to be higher in the child with Burkitt lymphoma than in the child's matched controls. This provided clear epidemiological evidence of a causal role of EBV in Burkitt lymphoma in Africa. The results of this study were confirmed when 51 out of 53 cases of Burkitt lymphoma from the whole West Nile District were found to have EBV particles in the tumour cells, while none were present in cases of other tumours.

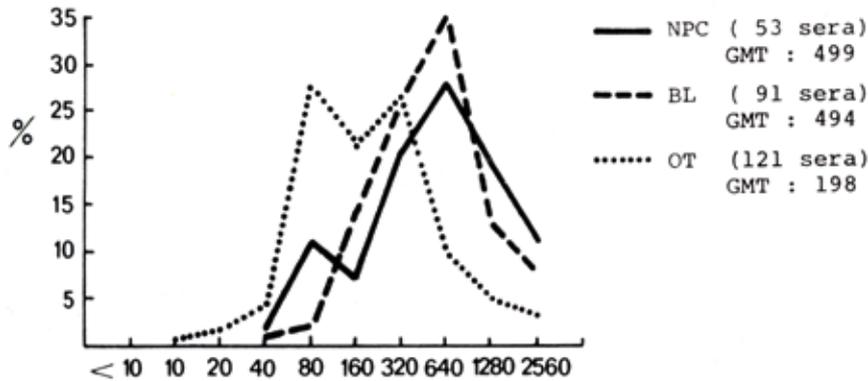


Guy de Thé, at left, with the field research team in Uganda. IARC epidemiologist Anton Geser is fifth from the left.



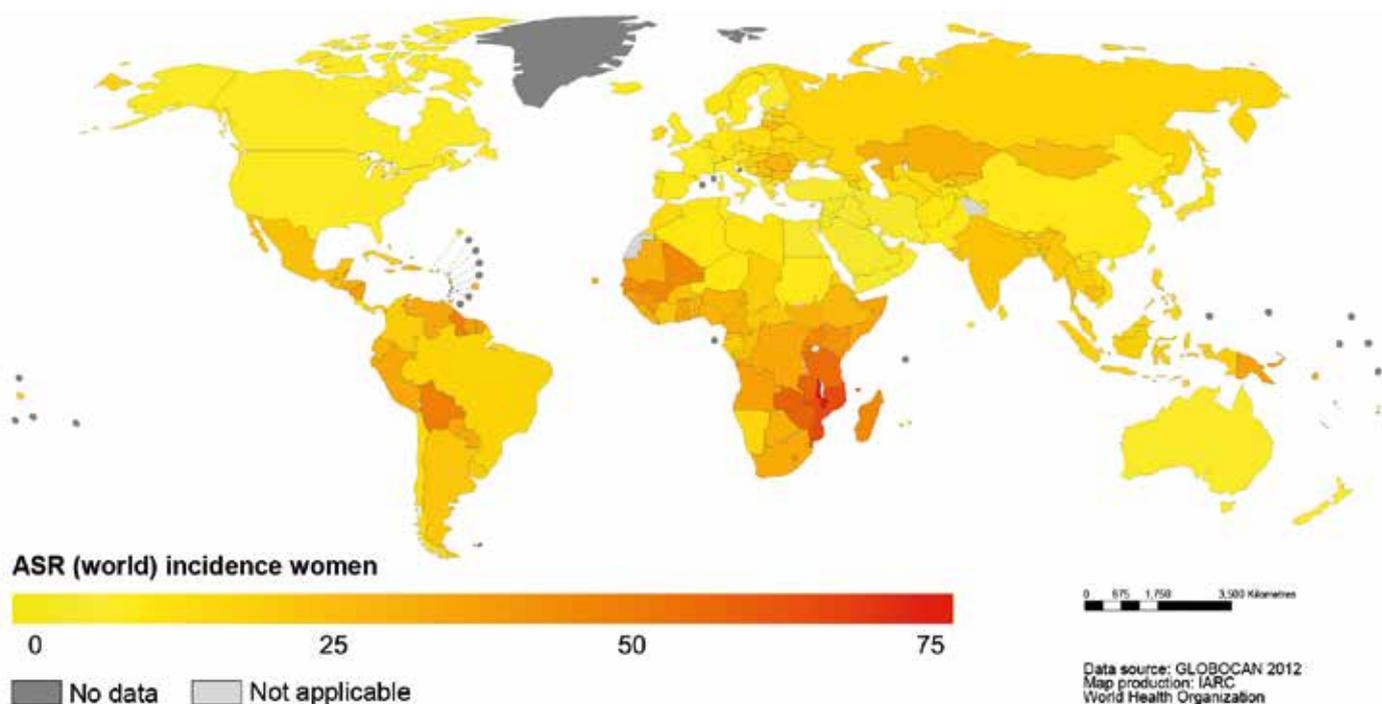
In most comparisons, levels of antibodies against the Epstein–Barr virus viral capsid antigen (EBV/VCA) were appreciably higher in Burkitt lymphoma (BL) cases (filled circles) than in their matched controls (open circles).

Evidence for a major role of EBV in Burkitt lymphoma in equatorial Africa emerged from the West Nile investigation in Uganda. In the meantime, Burkitt lymphoma was reported sporadically from continents other than Africa, but in those cases EBV was found in the tumour cells much less frequently. As was highlighted already in 1985 by the numerous papers in IARC Scientific Publication No. 60, *Burkitt's Lymphoma: A Human Cancer Model*, EBV acts in cooperation with other co-factors: probably impaired immunity due to malaria infection in cases from equatorial regions and multiple other co-factors in cases from other areas, as well as in nasopharyngeal cancers.



The vertical axis shows the percentage of subjects with different levels of antibodies against the Epstein-Barr virus (EBV), indicated by the numbers on the horizontal axis. High concentrations occur in a larger percentage of subjects with Burkitt lymphoma (BL) or nasopharyngeal carcinoma (NPC) than in subjects with other cancers (OT). GMT, geometric mean titre.

IARC laboratories have continued to study the mechanisms of action of EBV and its interaction with co-factors. Recent contributions have shown the relevance of tobacco smoking and of some genetic variants in nasopharyngeal cancer. In addition, some recent results point to a possible interaction between EBV and aflatoxin, a known carcinogen endemic in the regions where Burkitt lymphoma is commonly found in Africa (see the chapter "Carcinogens in the human environment"). The Working Group responsible for Volume 100 of the IARC Monographs evaluated as sufficient the evidence for the carcinogenicity of EBV for several tumours, including Burkitt lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, and nasopharyngeal cancer. Malaria as a co-factor in the etiology of Burkitt lymphoma had been investigated in an IARC study in the United Republic of Tanzania in the late 1970s. In 2012, the Working Group for Volume 104 of the IARC Monographs categorized malaria caused by infection with *Plasmodium falciparum*, the parasite present in highly endemic areas, as probably carcinogenic to humans.



*The map shows a large global variation in the incidence of cervical cancer in 2012. ASR (world) is the age-standardized rate (new cases per 100 000 women per year), standardized for age using the world standard population.*

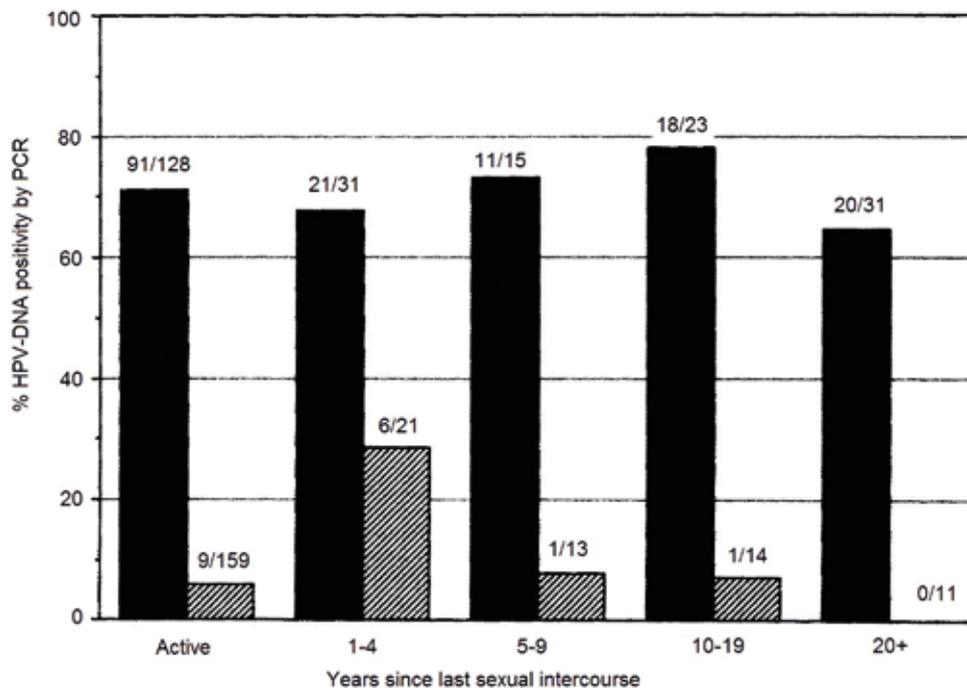
The initial focus of IARC scientists on EBV also prompted research on the most frequently occurring tumour in women in developing countries: cancer of the uterine cervix. This tumour was a rather obvious candidate for having an infectious cause. Several studies had documented its association with the number of sexual partners of a woman or her husband. As Richard Doll and Richard Peto wrote in 1981, “The present evidence strongly suggests that one of the primary causes of the disease is an agent passed between partners in intercourse, quite possibly a virus.” At IARC and in other laboratories, tests for EBV were conducted on serum samples of patients and on cervical cancer cells, with disappointing results. These investigations pointed to a need for an expanded search for relevant infectious agents, starting with other herpesviruses already known to be sexually transmissible.

### **HUMAN PAPILLOMAVIRUSES AND CANCER, ACT ONE**

The rhythms of research on cervical cancer at IARC have been marked by two interwoven developments: field epidemiological studies, periodically interspersed with syntheses of the accumulating evidence, including from IARC, on causes of this cancer. A 1989 IARC Scientific Publication already took stock of the changing direction in research, from fruitless efforts on herpesviruses to promising explorations of the role of human papillomaviruses (HPV) (see “1989: Cervical cancer and infection – growing evidence amid much uncertainty”). In several laboratories, considerable advances were made in the understanding of the

molecular mechanisms by which certain types of HPV could transform normal cells into cancerous cells. However, the epidemiology linking HPV to cervical cancer lagged behind.

It is at this juncture that IARC played a key role, mainly through a case-control study involving cervical cancer cases and randomly selected population controls in Colombia and Spain. The frequency of cervical cancer in Colombia was about 8 times that in Spain. Cells from cervical-swab specimens were tested for the presence of HPV DNA. In both countries, the percentage of positivity for HPV was much higher in cells from cases of invasive (i.e. advanced) cancer than in cells from control subjects, and this result was independent of whether the women were sexually active.



*Human papillomavirus (HPV) DNA was measured with polymerase chain reaction (PCR) in cervical cells. The percentage of women testing positive for the presence of HPV DNA was much higher among cervical cancer cases (black columns) than among controls (grey columns), regardless of the time since last sexual intercourse.*

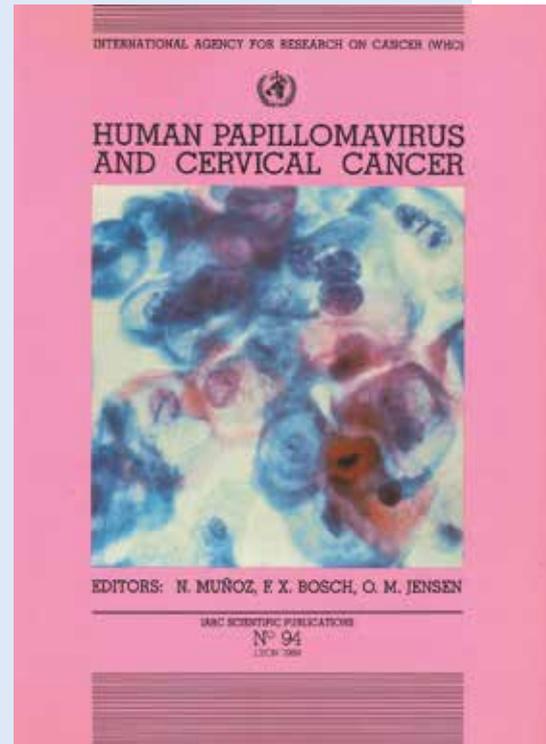
A second IARC study was conducted, also in Colombia and Spain, with less advanced cases of cervical cancer (carcinoma in situ). Again, a marked excess of HPV positivity was found among cases compared with controls. The strong association between HPV and cervical cancer, both at an early stage (carcinoma in situ) and at a later stage (invasive cancer), indicated that HPV infection precedes the full development of the tumour, strengthening the evidence for a causal rather than a “passenger” role of the virus.

## 1989: CERVICAL CANCER AND INFECTION – GROWING EVIDENCE AMID MUCH UNCERTAINTY

IARC Scientific Publication No. 94, *Human Papillomavirus and Cervical Cancer*, was published in 1989. The book's preface concisely summarizes how research trends were evolving at that time: "Although evidence for an association between cervical cancer and sexual activity has been available for over a century, the causal role of a sexually transmitted infectious agent has not yet been proven. For the last two decades attention has been focused on herpes simplex virus type 2 (HSV 2) as the main etiological agent and, although recent studies tend to dismiss this association, it cannot yet be excluded that this virus may play a role. It has only recently become possible to distinguish clearly HSV 2 type-specific antibodies from the closely immunologically related HSV 1 antibodies, and the new methods have yet to be applied in large-scale epidemiological studies.

"In the meantime, attention has shifted to certain types of human papillomavirus (HPV) as prime etiological candidates. The cloning of HPV DNA in bacteria about six years ago and the development of various hybridization methods for routine use have made possible assessment of type-specific exposure to HPV. ... In the light of the continuing debate about the role of HPV in cervical cancer and confronted by practical problems in the conduct of our own epidemiological studies, we decided to convene a small multidisciplinary meeting to evaluate critically the available epidemiological evidence on HPV and cervical cancer and to identify areas in which further epidemiological research is needed."

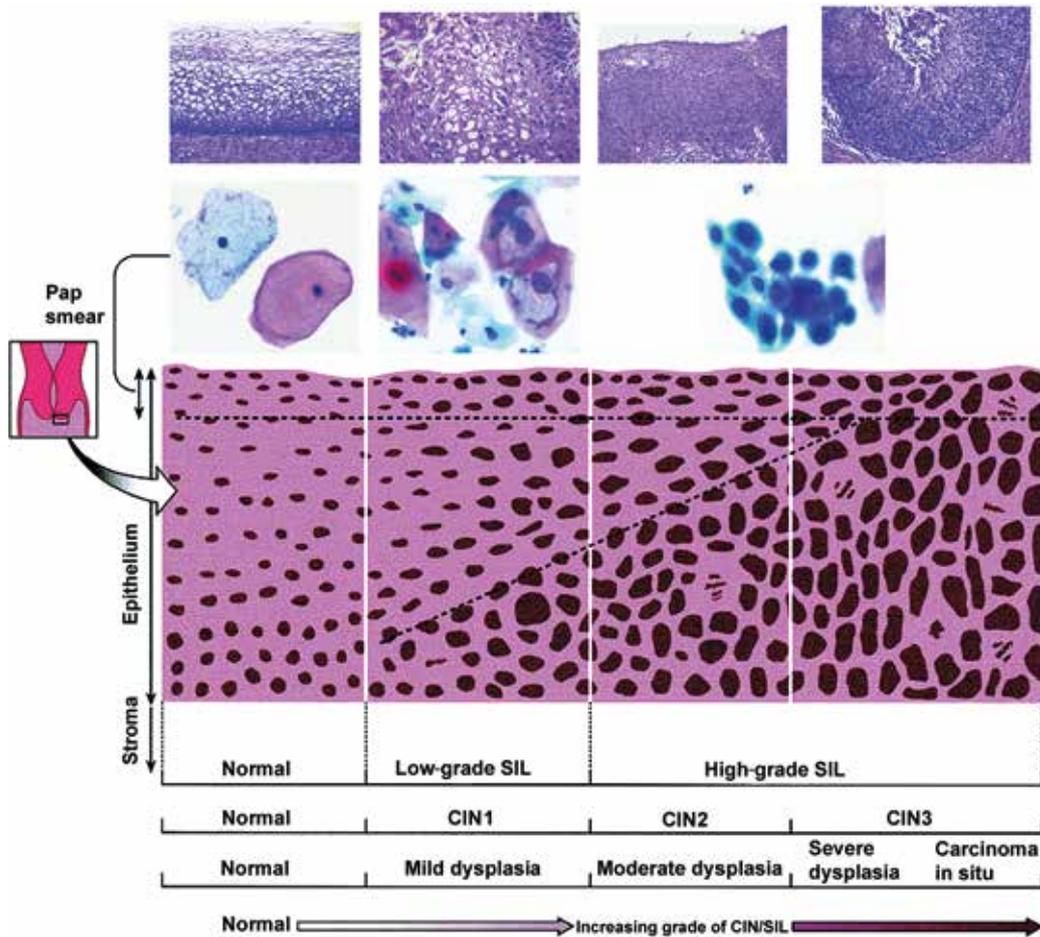
The volume concludes on a note of encouragement but, even more, of caution: "Current epidemiological studies are expected to provide clear evidence on the association between HPV and cervical cancer (IARC Annual Report, 1985, p. 57). The available data, although suggestive, do not allow further inferences on causality. Epidemiologists embarking on studies in this field should establish close collaboration with molecular biologists and clinicians in order to make the best use of the recent advances in each of these branches of biology and medical science."



Six years after the 1989 IARC publication, the prevailing views on HPV and cervical cancer had changed radically. The Working Group for Volume 64 of the IARC Monographs, *Human Papillomaviruses*, concluded that there is sufficient evidence for the carcinogenicity of HPV types 16 and 18, the subtypes that most frequently infect cervical cells. In 2008, Harald zur Hausen, whose laboratory in Heidelberg produced key experimental evidence on the carcinogenicity of HPV, received the Nobel Prize “for his discovery of human papillomaviruses causing cervical cancer.” The crucial epidemiological demonstration that some HPV types indeed cause cervical cancer in humans earned Nubia Muñoz, the lead scientist of the IARC studies, several prestigious recognitions around the world.



*Nubia Muñoz received the Gairdner Foundation's Canada Gairdner Global Health Award in 2009. The award was conferred “for her epidemiological studies that defined the essential role of the human papillomavirus in the etiology of cervical cancer on a global level, which led to the development of successful prophylactic vaccines.” Seen at the awards ceremony are, from left to right, John Dirks, president and scientific director of the Gairdner Foundation, the Ontario Minister of Health, Nubia Muñoz, and the deputy director of the Gairdner Foundation.*



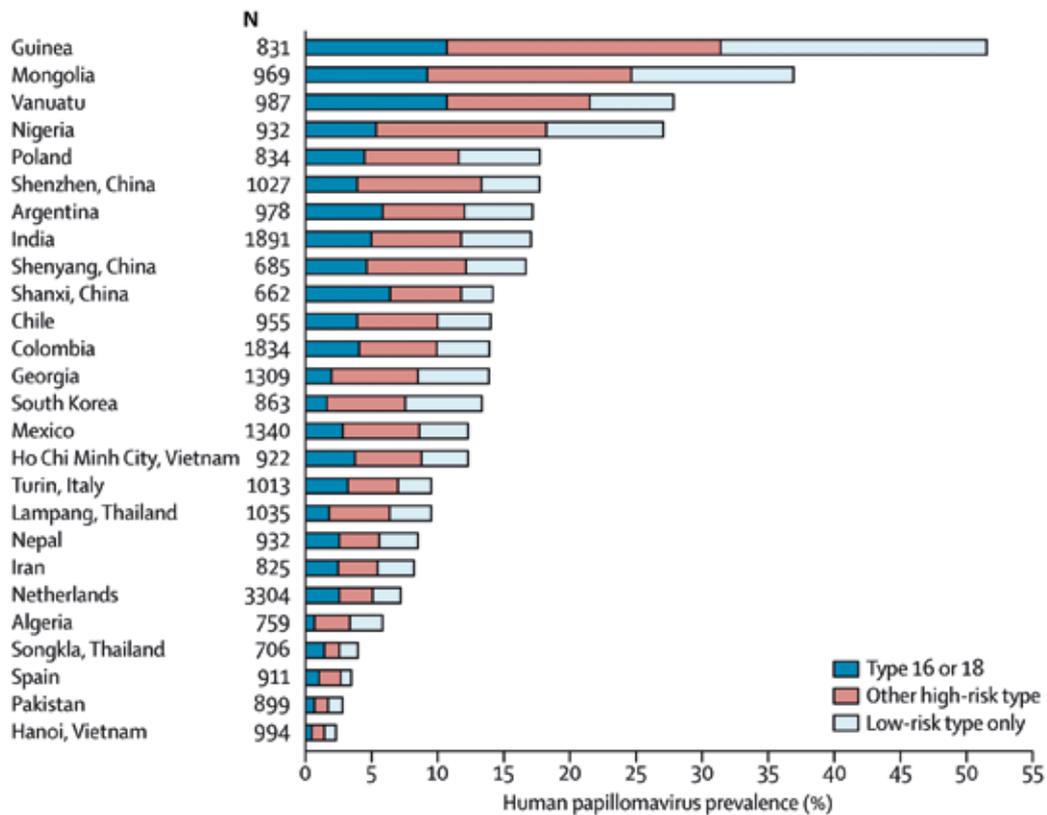
*This diagram illustrates the progression from normal tissue of the uterine cervix to carcinoma in situ, the earliest stage of cervical cancer, via a series of steps dependent on the persistence of human papillomavirus (HPV). From top to bottom are shown the microscopic appearance of the tissue, the appearance of the exfoliated cells used for the Pap smear screening test, a schematic representation of the progressive changes in the tissue, and the terminology for the stages of progression (CIN, cervical intraepithelial neoplasia; SIL, squamous intraepithelial lesion).*

## HUMAN PAPILLOMAVIRUSES AND CANCER, ACT TWO

Establishing that HPV causes cervical cancer opened up entirely new perspectives in research, aimed at preventing the occurrence of the cancer or controlling it through early diagnosis and treatment. The scientific basis for the production of preventive vaccines acting against virus-like particles of HPV had been established during the 1990s, and vaccines approved for use in human populations were made available by the pharmaceutical industry starting in 2006. However, deciding who should be given the vaccine, and when, demanded a thorough knowledge of the natural history of HPV infection. Most sexually active individuals of both sexes acquire HPV infection at some time during their life, but more than 90% of new infections regress over 6–18 months. In the remaining 10% of cases, infection persists, and in some women cells may progress to precursor lesions and ultimately to invasive cervical cancer. To sustain this evolution, other factors (viral, host, or environmental) must play a role. Tobacco smoking is the best-established co-factor, as a result of several epidemiological studies from IARC and other research groups.

Which population should be eligible for vaccination? A study by the International Collaboration of Epidemiological Studies of Cervical Cancer was coordinated by IARC and published in 2012. The results showed that although women can be infected by carcinogenic HPV at any age (with most infections occurring soon after first intercourse), the risk of cervical cancer arising from a new infection falls sharply with age and is very low after about age 40, an indication that vaccination efforts should focus on young people.

Another recent collaborative study, initiated by the United States National Cancer Institute, was conducted in Costa Rica. Healthy women aged 18–25 years were randomized to receive vaccination against HPV types 16 and 18 or vaccination against hepatitis A virus. After 4 years of observation, the HPV vaccine showed a high efficacy in preventing the occurrence of high-grade precursor lesions. A third IARC study used a mathematical model of the transmission of HPV 16 and 18 to investigate the impact of different vaccination options in high-income countries. It concluded that maximizing vaccination coverage of girls is currently the most effective option for decreasing HPV infection of the cervix, rather than aiming at vaccination of boys and girls.



IARC's international surveys of prevalence of human papillomavirus (HPV) infection were carried out from 1995 to 2013 in sexually active women aged 15–59 years. N denotes the number of women tested.

The study in Costa Rica and an ongoing IARC-coordinated randomized trial of HPV vaccine in rural India have shown that two doses of the vaccine are as good as the standard three-dose schedule in providing immunity and preventing infection of the cervix with HPV. This important observation will make implementation of HPV vaccination more affordable and has led to World Health Organization (WHO) support for a two-dose schedule. As the HPV vaccine becomes more affordable, more countries are assessing the potential benefits with regard to cervical cancer prevention for their own populations. One of the pieces of evidence needed for evidence-based policy-making is the prevalence of HPV subtypes in cervical tumours from patients in the country concerned. IARC has helped inform such considerations with its HPV prevalence survey, which uses a standardized protocol and analytical methodology applied to different populations worldwide to provide such information. To date, results are available for 27 populations across the world. The frequency of HPV infection varies widely, from 3% in Spain to 15% in Colombia and to the very high prevalence of more than 50% in Guinea.



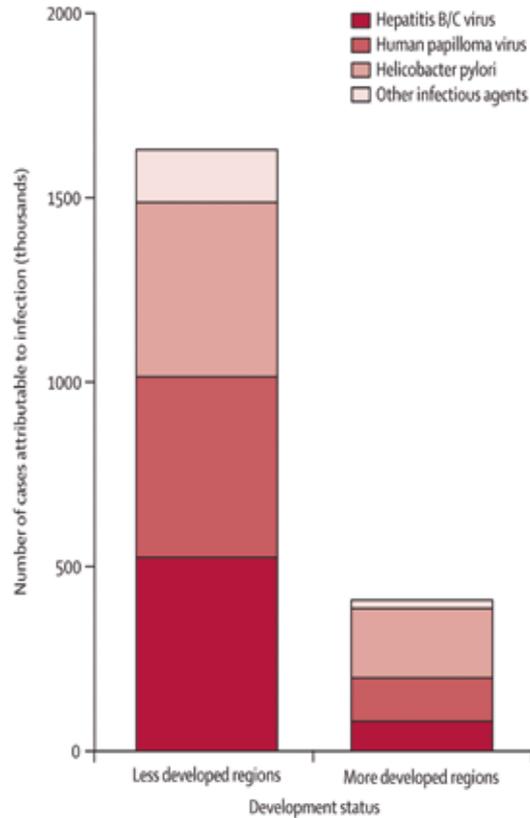
This phylogenetic tree of 100 human papillomaviruses shows how the types are genetically interrelated. The types in the alpha species for which the best evidence of carcinogenicity exists are shown in orange.

Different types of HPV vaccines are commercially available or in preparation. The rapidly increasing availability of these vaccines has not obviated the need for early diagnosis of cervical cancer in unvaccinated women. The Pap smear, the well-established screening method for cervical cancer, may now be preceded or superseded in many countries by testing for the presence of HPV DNA, thus improving the overall quality of a screening programme (see the chapter “Cancer screening and early diagnosis”).

In principle, HPV subtypes other than types 16 and 18 could also be carcinogenic, and organs other than the cervix could also be affected. In 2009, the Working Group for Volume 100B of the IARC Monographs reviewed all the available evidence. As the figure shows, several other subtypes in the alpha species, to which the carcinogenic subtypes HPV 16 and 18 belong, also cause cancer, and in particular cervical cancer. HPV 16 was concluded to cause not only cervical cancer but also cancers of other genital organs (vulva, vagina, penis) and of the anus, oral cavity, oropharynx, and tonsil. A recent IARC study observed wide variations in the proportion of oropharyngeal cancers associated with HPV infection in different populations worldwide. This finding will be important in assessing the future benefits of vaccination on cancers at sites other than the cervix.

IARC scientists are currently studying another family of papillomaviruses, the beta subtypes. The beta species may play a role in skin cancer, where there are, once again, possible interactions with environmental co-factors, such as ultraviolet radiation. Comparisons of the similarities and differences with the alpha subtypes assist in understanding how these and other viruses trigger the development of cancer.

Overall, it is estimated that worldwide, more than half a million new cancer cases per year are attributable to infection with HPV, about the same as the number of liver cancer cases caused by infection with hepatitis B and C viruses. Therefore, HPV infection has been proven to be an important cause of cancer. IARC has been part of the remarkable success story in translating that knowledge into the potential to prevent a substantial proportion of those cases.



*Number of new cancer cases per year attributable to infections, subdivided by infectious agent and degree of development of world regions.*

## LIVER CANCER

The spark of Burkitt's keen clinical observations on lymphoma, followed by the discovery of EBV, was the first time that there was evidence for the carcinogenicity of a virus in animals and humans. For liver cancer in humans, the identification of causal factors took much longer. The first volume of the IARC Scientific Publications series, *Liver Cancer*, contains the proceedings of a conference held in London in July 1969. The proceedings document the mixture of well-established facts, dubious or fragmentary findings, and mere conjectures that prevailed at the time (see "Liver cancer as seen in 1969"). From the outset, IARC started to take advantage of what was already known to probe the etiology of liver cancer. Several research projects were developed on aflatoxins, experimentally recognized as carcinogens, to investigate their possible role in human cancer (see the chapter "Carcinogens in the human environment").

As soon as reasonably reliable markers of hepatitis viruses, particularly of hepatitis B virus (HBV) infection, became available, IARC epidemiologists led or participated in case-control studies of liver cancer. The results showed a clear association with the HBV markers, and pointed to the role of tobacco smoke as a subsidiary etiological factor. Indeed, by the early 1980s the accumulating evidence from both case-control and cohort studies had shown that the association between HBV infection and liver cancer was strong, specific, and consistent, but was restricted to chronically persistent forms of HBV infection. Most epidemiologists accepted the association as being causal, although substantial proportions of liver cancer did not exhibit the HBV markers.



*There was not (and still is not) a vaccine against EBV. Hence, the issue at stake was to test the first anticancer vaccine.*  
– Christian Trépo, long-term IARC collaborator

The idea rapidly gained ground that a study of subjects vaccinated against HBV would be valuable for several reasons: it would prevent hepatitis B, it would be the acid test of whether HBV was a cause of liver cancer, and – should this prove to be the case – it would prevent the occurrence of this tumour in the population under investigation.

HBV is one of the most common infectious viruses in the world, and vaccines of different types had been available against HBV since 1969. To test the vaccine's effectiveness in preventing liver cancer, a population was required in which HBV infection rates were high and liver cancer was common. Of

the countries in sub-Saharan Africa with these characteristics, The Gambia presented a suitable option. In the mid-1980s, The Gambia had a population of a little more than 1 million people and a reasonable infrastructure.

## LIVER CANCER AS SEEN IN 1969

The “working conference” on liver cancer convened by IARC in London in 1969 was chaired by Sheila Sherlock, a leading clinician and researcher on liver diseases. In 1956, Peter Magee had demonstrated for the first time that nitrosamines can induce liver cancers (hepatocarcinomas) in the rat (see the chapter “From laboratory to population”).

In Magee’s conference paper, he noted: “The remarkable differences in cancer incidence in different parts of the world are well known. Primary liver cancer is a notable example of such differences in geographical distribution; it is particularly common in Africa south of the Sahara and, to a lesser extent, among the Chinese in Singapore. ... It thus seems highly probable that the remarkably high incidence of liver cancer in certain areas, especially in Africa, must be the result of environmental factors, often of quite sharply localized geographical distribution. Among the main known causes of cancer – radiation, viruses and chemicals – it seems unlikely that radiation is an important factor. The possible role of preceding viral hepatitis in the etiology of liver cancer has been discussed by Higginson (1963), who concludes that the combined evidence is not convincing. *Furthermore, as yet there appears to be no definitely proven example of a human cancer induced by a virus* [italics added]. The third possibility – namely, the presence of chemical carcinogens in the environment in areas of high liver cancer incidence – must therefore be seriously considered, and this paper is concerned with such a hypothesis. A logical corollary of this hypothesis would be that in areas with populations of similar genetic structure but low liver cancer incidence, the postulated environmental hepatocarcinogens should be absent, or present in much lower amounts.” Magee then went on to review the existing evidence for the carcinogenicity of several environmental carcinogens for liver cancer in humans.

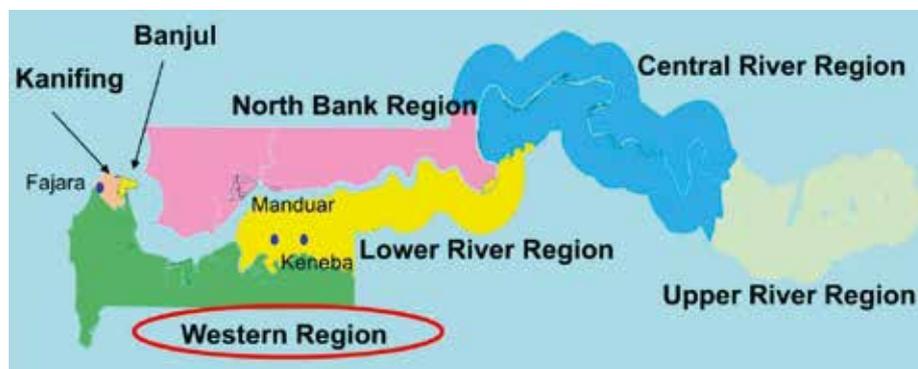
As highlighted by other contributors to the conference, the viral etiological hypothesis was gaining ground. For many years, hepatitis – in particular, the so-called serum hepatitis associated with blood transfusions and reuse of contaminated needles and syringes – had been known to be due to some “filterable” and transmissible agent, probably a virus that had remained unidentified. In 1965, Baruch Samuel Blumberg had discovered an antigen that initially seemed to be genetically determined but soon afterwards was shown to be characteristic of the surface of the newly identified serum hepatitis (or hepatitis B) virus. This antigen, which became known as the Australia antigen since it had first been isolated in the serum of an Australian Aboriginal person, made it possible to investigate the relationship between the virus and liver cancer by measuring several markers of the virus, namely the antigen itself or antibodies secreted against it.

Pulling together the threads from the conference presentations and discussions, the Subcommittee on Priorities in Human Carcinogenic Studies recommended that “priority should be given at this stage to linking already known or suspected carcinogenic factors ... rather than to discovering new factors, because considerable benefits can be reaped from the integration of data from studies already in progress.” In this vein, the subcommittee recommended both case–control and cohort studies to explore the relationship between the presence of the Australia antigen and the occurrence of liver cancer. It also recommended studies investigating the presence of carcinogens such as nitrosamines or aflatoxins, or their metabolites, in the urine of populations known to be at risk of developing liver cancer.



The frequency of infection with the hepatitis B virus (HBV), as measured by the presence of the Australia antigen (HBV surface antigen), shows wide variation throughout the world.

IARC established a multiparty research collaboration – the Gambia Hepatitis Intervention Study – in which it played the leading scientific role, in collaboration with the government of The Gambia, the United Kingdom Medical Research Council (which had a long-established research unit in Fajara, close to the capital city of Banjul), and the Italian government, which provided considerable funds.



A map showing the different regions of The Gambia in West Africa on the two banks of the Gambia River, which flows into the Atlantic Ocean at the Kanifing District. The Gambia Hepatitis Intervention Study covered the whole country, whereas the recently initiated Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) study is taking place in the Western Region.

It was known that in The Gambia the highly endemic HBV infection occurs by transmission during childhood, for example in the family or at school. Therefore, a vaccination programme was started in 1986, with a schedule of injections at birth and at the ages of 2, 4, and 9 months. The anti-HBV vaccine was incorporated into the existing Expanded Programme on Immunization recommended by WHO. The original design of the study – a “stepped-wedge” trial – was both scientifically and ethically sound (see the chapter “Innovation in statistical methods”). At the end of the fourth year of the vaccination campaign, two comparable groups, vaccinated and unvaccinated, of more than 60 000 children each had been recruited into the study. A series of logistic problems had to be overcome, including those arising from the staff (at the full complement, more than 80 people) belonging to three different organizations: IARC, the United Kingdom Medical Research Council, and the government of The Gambia. A clear indication of success is the 93% completeness of the vaccination coverage of the targeted population of children.

To follow up the study participants and record the liver cancer cases, the Gambia National Cancer Registry was established in 1986. It has been estimated that results adequate to measure the protective effectiveness of infant vaccination on adult liver cancer will emerge from the comparison of vaccinated and unvaccinated children 30–35 years after immunization, before 2020. Several valuable intermediate results have already

## How to measure the outcome (HCC)?

- Established the **Gambia National Cancer Registry** in 1986
- Linking HCC patients with vaccination database
  - Name
  - Sex
  - Year of birth
  - Birth place
  - Names of parents
  - BCG scar
  - Foot & palm prints



*Assessing the results of the Gambia Hepatitis Intervention Study involves linking the cases of liver cancer (HCC), recorded by the Gambia National Cancer Registry, with the vaccination database containing the listed items. Vaccinated people will be recognizable by the position of the scar from the antituberculosis bacille Calmette–Guérin (BCG) vaccine – given on the left forearm to people vaccinated against hepatitis B virus and on the right forearm to the unvaccinated – and by comparison of their current foot and palm prints with those taken in childhood.*

been gathered, the most important of which is the 94% protection that the vaccine shows against chronic persistence of the virus even 20 years after vaccination, indicating that there is no need for a booster dose in adolescence.



*WHO has just reviewed the long-term protection from hepatitis B vaccine, and produced a statement on global policy for whether or not a boost was required, and the only first-rate evidence they had was from the Gambia study. So it is still highly influential in terms of global policy-making. – Andrew Hall, former IARC scientist*

Studies showing combined effects of aflatoxin exposure and HBV carrier status have been informative in illustrating the potential benefit of interventions against aflatoxins, particularly for those individuals already chronically infected with HBV and therefore out of reach of the protection afforded by the vaccine. In the same vein, a new study has been started in The Gambia and Senegal. The Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) study aims to assess whether antiviral therapy can reduce the incidence of liver cancer in West Africa by identifying and treating chronic HBV carriers before their disease progresses to malignancy.

## LEARNING FROM VIRUSES

For research on cancer biology, viruses have proven to be an inexhaustible source of information on mechanisms of carcinogenesis. For instance, the first oncogenes (crucial genes that, when activated, can trigger malignant transformation of the cell) to be discovered were found to result from sequences of viral DNA inserted into the human genome by viruses over the course of evolution.

In the identification of causes of cancer, the discovery of carcinogenic viruses has been the most important breakthrough during the past 50 years, since IARC was established. This discovery was relevant for both science and health. Virally induced cancers represent a substantial burden, particularly in developing countries, and they can be controlled with preventive measures. According to IARC's most recent estimates of the global burden of cancer associated with infections, about 11% of new cancer cases worldwide are attributable to viral infections, and 16% to infections as a whole; in sub-Saharan Africa, one third of all cancers are infection-related. From its earliest years, IARC has made substantial contributions to the advances aimed at reducing this burden.

For IARC, the successes of its research on viral carcinogenesis and on the control of virus-induced tumours illustrate the value of combining three approaches, which reinforce each other. First, field studies that collect original data with the direct involvement of IARC epidemiologists, support from IARC laboratories, and a large international multidisciplinary collaboration facilitated by IARC's standing as a research organization within the WHO framework. Second, periodic authoritative reviews of the evidence pertinent to specific issues of importance in relation to causation and prevention – as have been done for the carcinogenicity of EBV, HBV, hepatitis C virus, and HPV – carried out by international experts under the auspices of IARC as an international agency. Third, an investment in the continuity of long-term research programmes that, although they evolve and adapt over the decades, remain fixed in their commitment to the original objective (see “IARC's long-term research projects in developing countries”).

#### **IARC'S LONG-TERM RESEARCH PROJECTS IN DEVELOPING COUNTRIES**

Andrew Hall, now Sir Andrew and emeritus professor at the London School of Hygiene & Tropical Medicine, was the IARC team leader in The Gambia for 5 years when the vaccination programme of the Gambia Hepatitis Intervention Study was initiated. He expresses his views on the value, challenges, and requirements of long-term research projects in a developing country.

“My role was to lead that project in the field. We had a clearly defined, sizeable budget, which came through IARC from the Italian government, and the vaccine was donated by a vaccine manufacturer. We trained all the Gambian health workers, and we introduced in a phased manner the anti-hepatitis B virus vaccine into the routine vaccination programme of The Gambia. In addition, we set up a national cancer registry for the country, in order to provide the means of evaluating the outcome over the coming 35 years.

“The challenge over the long term has been maintaining interest, maintaining the quality of the data, maintaining staff, replacing staff, and of course, for IARC, maintaining a budget. The changes of IARC Directors over such a long period have led to some ups and downs in the project management from Lyon.

“As to the national cancer registry, it has continued to struggle, largely because the health system infrastructure, as in so many low-income countries, is inadequate. ... If you work with these countries, the demand for resources is almost bottomless, and so you have to find ways of doing things that can be managed with the limited resources that the country has.

“IARC has a problem to tackle because the countries that become its members and support it are the wealthier countries of the world, while the countries that need the help the most are the poorest countries. So IARC has to persuade the wealthy countries that the money is taken from them but is spent mostly in the poor ones. I think this is essential for reducing the inequalities we see around the world.

“These projects are important. Things have changed since we began the study in The Gambia. It would not be appropriate today to put expatriates into a country; now, nationals with the pertinent skills should be recruited and one should work jointly with them.”



*Andrew Hall, who led the Gambia Hepatitis Intervention Study for IARC from 1986 to 1991.*

