

COMMENTARY

PROLIFICA: a story of West African clinical and research collaborations to target hepatitis B-related hepatocellular carcinoma in West Africa

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HBV infection and hepatocellular carcinoma in West Africa: size and scope of the problem

Hepatitis B virus (HBV) infection is highly endemic in sub-Saharan Africa, where the lifetime risk of HBV infection is over 60% and more than 8% of the population remains chronic HBV carriers. Furthermore, this area has one of the highest HBV-related liver cancer rates in the world,¹ being the most common cancer in men and third most common in women.^{2,3} HBV infection therefore represents a significant global threat to health in the African continent.

Though most countries in sub-Saharan Africa have established HBV vaccination programs for infants through the WHO and Global Vaccine Alliance (GAVI)-sponsored Expanded Program of Immunization, HBV vaccine coverage remains incomplete.⁴ Furthermore, the current recommendation from World Health Organisation African division (WHO-AFRO) for birth dose HBV vaccination to prevent maternal-child transmission and early horizontal transmission of HBV has not been widely implemented.⁵ This is a critical issue in Africa, as more than 90% of children infected with HBV early in life progress to become chronic carriers of HBV, with the attendant risks of HBV-related liver disease, liver cancer and death.^{6,7}

Severe limitations in healthcare infrastructure, availability of diagnostics and treatment mean that currently West Africa is ill-equipped to manage the exponentially increasing burden of disease relating to the HBV epidemic. Greater knowledge of the determinants of hepatocellular carcinoma (HCC) development and cost-effective point-of-care diagnostic tests for HBV-related liver disease, and HCC are significant unmet needs in West Africa.

Hepatitis B research collaborations between West Africa, Europe and the UK

Since 1973, HBV research has been conducted in Gambia, West Africa, through collaborations between MRC Gambia, Imperial College London and the London School of Hygiene and Tropical Medicine. Initially, this comprised a HBV natural history study of a longitudinal cohort of patients in two villages, Keneba and Manduar, in the West Kiang district.⁸ Two hundred and sixty-five HBsAg positive subjects identified from this study have been followed up with regular serosurveys for more than 20 years, making this one of the largest and most complete HBV natural history studies of its type worldwide.

Received: 27 January 2015; Revised (in revised form): 12 June 2015

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This study has provided key information on HBV prevalence and the epidemiology of HBV transmission in West Africa as well as vital information on HBV-related HCC incidence and risk factors.⁸

Following this, a second large cohort study, the Gambian Hepatitis Immunization Study, was a pilot study of HBV vaccination effectiveness at preventing both HBV chronic carriage and HBV-related HCC in The Gambia, conducted in 120 000 children.^{9,10} Study findings supported widespread implementation of HBV vaccination of infants through the GAVI-sponsored expanded program of immunisation in West Africa.

Data from these important studies provided the impetus for development of a large, multicentre trial to explore the burden of HBV-related liver disease and liver cancer in West Africa and simultaneously pilot and evaluate a screening and treatment program for HBV-related liver disease and liver cancer. The European Union Framework 7-funded multicentre Prevention of Liver Fibrosis and Liver Cancer in Africa study (PROLIFICA), an extensive multicentre collaboration between Medical Research Council (MRC) Gambia, International Agency for Research in Cancer (IARC) (France), Imperial College London (UK), Jos University (Nigeria) and Cheikh Anta Diop University (Sénégal) was launched in Banjul, Gambia in 2011 (Figure 1) to fulfill these objectives.

The PROLIFICA study comprises two arms: HC4 and WATCH: HC4 is a large case-control study of HBV-infected subjects with and without HCC, aiming to determine novel genetic, proteomic and metabolomic biomarkers for HCC diagnosis and prognosis

that can be developed into affordable point-of-care tests suitable for use in resource-poor settings.¹¹

The WATCH study is a longitudinal study comparing the incidence of HCC among HBsAg positive subjects who commence HBV treatment with the antiviral nucleoside analogue, tenofovir as per European Association for the Study of the Liver (EASL) international guidelines,¹² compared with those who do not. Subjects receive full assessment of their HBV-related liver disease including Fibroscan. This HBV screening, liver disease assessment and treatment programme represents the first of its kind in Africa and over 13 500 people have been screened for HBsAg to date.

In parallel to research relationships in The Gambia, a fruitful relationship between Jos University, Nigeria and Imperial College, London, was fostered initially through an upper endoscopy educational training exchange programme supported by the Royal College of Physicians,¹³ in which Prof. Simon Taylor-Robinson from Imperial College, London and Dr Nimzing Ladep from Jos University Nigeria took part. After a further Royal College of Physicians educational exchange at the Hammersmith Hospital in London in 2009, Dr Ladep started nationwide endoscopic retrograde cholangiopancreatogram (ERCP) services with gastroenterology trainees from around Nigeria. Additionally, specialist nurse Mary Crossey undertook training of specialist liver nurses in Jos, supported by the Sir Halley Stewart Trust. A further Association of Physicians 'Links with Developing Countries' grant provided important support for a preliminary metabolomic biomarkers in HCC research platform between Jos University and



Figure 1. PROLIFICA group at the project launch in Banjul, 2011.

Imperial College London, that was subsequently incorporated into the PROLIFICA program.

Project outcomes and achievements

To date, the PROLIFICA study has provided important insights into HBV-related HCC in West Africa, including identification of novel metabonomic biomarkers which may prove useful for HCC diagnosis in resource-poor settings, identification of genomic determinants of HCC and epidemiological insights into risks for more severe HBV-related liver disease.¹⁰

Beyond these scientific discoveries, PROLIFICA has provided several critical developments for the region. The study has provided access to previously unavailable HBV treatment for non-HIV infected patients in West Africa and critical data on the cost-effectiveness of HBV treatment to inform health policy in sub-Saharan Africa. A Fibroscan has been provided both for Gambia and Sénégal for assessment of liver fibrosis, along with training of local personnel in its use. Training and education has been a cornerstone of the project, providing local staff and students with laboratory and clinical skills, research opportunities and mentorship, new technologies and improved infrastructure, including a mass spectroscopy system in Gambia for biomarker discovery at a regional West African level. Above all, strong relationships for future research collaborations have been developed. These are arguably the greatest achievements yielded from this project.

Conclusion

The PROLIFICA study is just one example of how successful international research collaborations can be between developed and developing countries in terms of high-quality research output, local infrastructure development and real educational opportunities for all parties. It also illustrates how relationships supported by smaller research grants and scholarships can lead to far greater things.

Acknowledgements

We are grateful to the Association of Physicians of Great Britain and Ireland for the initial 'Links with Developing Countries' grant. PROLIFICA is funded by the European Union Framework 7 programme (PROLIFICA: Prevention of Fibrosis and Liver Cancer in Africa). Dr Howell is supported by a National Health and Medical Research Centre (NHMRC Australia) Early Career Fellowship. Dr Ladep is supported by the British Medical Research Council ICIC scheme. Mary M.E. Crosse is supported by a fellowship from the Sir Halley Stewart Foundation, Cambridge, UK. All authors are grateful for infrastructure support provided by the UK National Institute for Health Research (NIHR) Biomedical

Facility at Imperial College London, London. MRC Gambia Unit provided infrastructure support for the PROLIFICA programme in Gambia. We are grateful to Mr Matthew Foster (Head of International Affairs at RCP London) for facilitating the initial contacts that led to PROLIFICA and to Prof. Roger Williams for useful discussions when he was Director of the International Office of the RCP London.

Conflict of interest. None declared.

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