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Harnessing the Power of Next Generation Sequencing to Decipher *Helicobacter pylori* Epidemiology, Pathogenesis and Genetics in Sub-Saharan Africa

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Helicobacter pylori (Hp) is one of man's most successful bacterial colonizers. It has been associated with this host for over 100, 000 years (1) and often infecting it for lifetime. It is estimated that 50% of the world population are infected by *Hp*. However, this prevalence is highly variable ranging from <10% to >90% with large differences between countries and between communities within the same country (2). *Hp* infection is asymptomatic in the majority of cases. In a small proportion of individuals, the infection leads to various diseases including peptic ulcers, chronic atrophic gastritis, gastric cancers, and gut lymphoma (3). Study of *Hp* biology from since discovery by Warren and Marshall in 1982 was associated with enigmas that are still being addressed. In low-income-countries of the world, one of these puzzles, which partly persists, is the association of high *Hp* prevalence and low incidence of gastric cancer (4). There are several factors in play regarding *Hp* pathogenesis including environment, diet, host and bacterial genetics (3). However, it remains unclear how these factors act and interact with each other. It is now well established that gastric cancer caused by *Hp* depends on the presence of the cag pathogenicity island which codes for CagA, classified as a primary carcinogen (3). Other virulence factors involved in *Hp* pathogenesis have been identified (2). In fact, *Hp* strains can be classified into two groups on the basis of two important virulence factors. Virulent strains, known as type I, possess the *cag* pathogenicity island and express an active form (s1/m1) of the vacuolating cytotoxin (VacA), while avirulent type II strains lack the cag PAI and express a benign form (s2/m2) of VacA (5). Although*Hp* is now formally classified as a true pathogen, the association of cag-negative, non-carcinogenic type II strains with possible benefits is still debated.

In Africa, risk factors for *Hp* infection including socioeconomic conditions, poor hygiene, and promiscuity are high. Consequently, the prevalence of *Hp* carriage is estimated at around 80% (6). However, reports onthe prevalence and incidence of *Hp* on the continent vary considerablyfrom region to region, with some countrieshavinghigh-quality studies, whereasfor most countries in sub-Saharan Africa (sSA), data are scarce or non-existent. Additionally, most reports concern individuals who developed clinical symptoms, and were included in surveys aiming to look for the presence of *Hp*. Data on*Hp* carriage in healthy people and on early detection of this bacteriumare scarce. However, knowledge of asymptomatic carriage of *Hp* is important because, in additionto the diseases it directly causes, it can promote or aggravate other conditions such as diabetes and heart diseases (7). On the other hand, some studies suggest that *Hp* may protect against diseases such asthma (8). The high prevalence of *Hp* carriage in Africa provides an opportunity for studies to decipher the negative and positive effects of *Hp* carriage. In sSA, there is a huge knowledge gap in several aspects of *Hp* epidemiology, pathogenesis, genetics and resistance to antibiotics used for treatment. This situation is due to the lack of bacteriology laboratories properly equipped to undertake *Hp* culture and characterization, and to the shortage of well-trained microbiologists. This greatly affects the management of *Hp* infection with empirical antibiotic therapy routinely applied, leaving clinicians with limited alternatives in the event of treatment failure. The current era of high-throughput sequencing and genomics constitutes an ideal context for advanced genetic characterization of *Hp* strains circulating in Africa. The *Hp* Genome Project, an international initiative to carry out genomic analysis of *Hp* strains recently released a publication that reported the analysis of 1011 isolates from 50 countries worldwide (9). Only 31 of these strains came from sSA. This shows the need of Africa-focused initiatives to undertake genomic analysis of *Hp* isolates circulating in this continent. There are many reasons that explain the scarcity of genomic data of African *Hp* isolates including the lack of sequencing equipment, the high cost of reagents and consumables, scarcity of bio-informaticians trained to process of high throughput sequencing data and of microbiologists able to properly analyze and interpret genomics results. There are a few programs that were established to address these gaps including the African Pathogen Genomic Initiative (APGI) and SEQAFRICA (10). APGI was launched by the African Centres for Disease Control (ACDC) and Prevention in 2020 in response to the threat posed by the SARS-CoV-2 pandemic. APGI greatly contributed to build capacity in genomicsby helping acquisition of sequencing equipment, procurement of reagent and training of technicians, virologists and bio-informaticians. Importantly, APGI also built a network of scientists that exchanged skills and ideas. As a result, the number of SARS-CoV-2 genomes sequenced in African laboratories increased from 5, 000 to +120, 000 from early 2020 to April 2023. Following the success of APGI, ACDC recently launched APGI 2.0, which aims to continue build genomic capacity in African countries and extended genomic analysis to microbial pathogens other

than SARS-CoV-2, including bacterial species. SEQAFRICA is another African-dedicated genomic initiative that was established in 2018 with funding from United kingdom's Fleming Fund regional grant. It aimed to introduce whole genome sequencing (WGS) and genomic analysis into the surveillance of antimicrobial resistance in sSA. During its first phase (2019-2023), four WGS Reference centers were selected, equipped with sequencing equipment and their bio-informaticians trained to perform genomic analysis. SEQAFRICA offers sSA laboratories the possibility to have their isolates sequenced and analyzed free of charge. Itsupported WGS and genomic analysis of +30, 000 bacterial and SARS-CoV-2 isolates from 22 sSA countries. Interestingly, SEQAFRICA especially focuses on the analysis of genetic determinant of antimicrobial resistance. Its second phase will be dedicated to bacterial isolates across sSA.

The second phases of APGI and SEQAFRICA offeran opportunity to include *Hp* as a target for WGS and genomic analysis. Existing biobanks of *Hp* isolates, with good quality metadata, collected across Africa could be included. Additionally, clinical gastroenterologists could be invited to join prospective investigations in which isolates recovered from biopsies of patients of *Hp*-caused diseases will be sequenced and analyzed. The collection of demographic and clinical data will be an important component of these projects, which will enable to correlate genomic features with diseases. The data that will be generated will be useful for public health, including the early phases of disease development, contribution of environmental and host factors, the impact of *Hp* infection on other diseases, and the potential benefits conferred by *Hp* carriage. Importantly, genomic analysis will shed light on the genetic determinants of antimicrobial resistant of the isolates and contribute to guide antibiotic treatment of *Hp* infection.

Conflict of interest: Dr Yakhya Dieye is the head of the Pole of Microbiology, part of the SEQAFRICA Regional Genomic Reference Laboratory at the Institut Pasteur de Dakar

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