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Review:

# Joint Research Project on Infectious Diseases in West-African Subregion

Eiji Ido<sup>\*,\*\*</sup>, Takashi Suzuki<sup>\*,\*\*</sup>, William K. Ampofo<sup>\*\*\*</sup>,  
Irene Ayi<sup>\*\*\*</sup>, Shoji Yamaoka<sup>\*</sup>, Kwadwo A. Koram<sup>\*\*\*</sup>, and Nobuo Ohta<sup>\*</sup>

<sup>\*</sup>Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University  
1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan  
E-mail: Matata.vip@tmd.ac.jp

<sup>\*\*</sup>Ghana-Tokyo Medical and Dental University Research Collaboration Center, Legon, Ghana

<sup>\*\*\*</sup>Noguchi Memorial Institute for Medical Research, College of Health Sciences,  
University of Ghana, Legon, Ghana

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A research collaboration project in Ghana has joined the MEXT program supported by the Japanese government since 2008. The Noguchi Memorial Institute for Medical Research (NMIMR), the University of Ghana, and Tokyo Medical and Dental University (TMDU) are core parties in the project, and researchers from other institutions also participate temporarily. Two TMDU faculty members are sent to Ghana to manage and implement joint research projects for virology and parasitology, which cover HIV, African trypanosomes, malaria parasites, and vector insects. Along with joint research, mutual exchange activities for young researchers and students have been promoted to develop human resources in tropical infectious disease research. Subjects in our project are all public health concerns both in Ghana and West-Africa and in other parts of the world. Our joint projects have strengthened and promoted global information networks on infectious diseases and the health and welfare of the residents of Ghana and Japan.

**Keywords:** Ghana, Noguchi Memorial Institute for Medical Research, HIV, African trypanosomiasis, vector research

## 1. Introduction

To establish a consolidated global research network on infectious diseases, Africa has clearly important roles as the source of clinical/epidemiological information on numerous maladies. Disease profiles in Africa are heterogeneous and some are particularly clinically important because of disease severity. Some diseases previously thought to be Africa-specific are no longer restricted to the continent and are now spreading to other tropical areas worldwide. The world-wide HIV/AIDS pandemic of the last century and sweepingly rampant outbreaks of West Nile virus infection in the United States in the 2000s [1] are good examples of such expanding global illnesses.

Thus, any information on communicable diseases is vital both in endemic countries and in developed countries considering recent dramatic increases in human migration in South-North trading and global tourism. One urgent matter to be considered is to establish a new system for collecting and managing information on infectious diseases at endemic sites, and therefore this Ghana-Japan project was started based on these expectations from both sides.

In Ghana, located in West-Africa, endemic infectious diseases are variable and unique. Residents are at risk for hemorrhagic viral infections, malaria, HIV, and “neglected” tropical diseases such as African trypanosomiasis, almost all of which are, however, preventable or controllable if residents are aware of accurate epidemiological information and of how to interrupt transmission. The aim of the Ghana-Japan joint project is to uncover infectious diseases and to propose recommendations and/or tools for controlling these diseases. In parallel with research, the development of human resources in infectious disease research has been implemented in both Ghana and Japan.

In this review, we will introduce research outcomes from our Ghana-Japan joint program.

## 2. Noguchi Memorial Institute for Medical Research

Our Ghana-Japan collaboration project was established at the Noguchi Memorial Institute for Medical Research (NMIMR), which was founded by donations from the Japanese government in 1979 (Fig. 1). NMIMR was initially a semiautonomous University of Ghana institute but is now integrated into the College of Health Sciences, University of Ghana. The Institute is in East Legon, a northern suburb of Accra, Ghana’s capital city. NMIMR was named for Dr. Hideyo Noguchi, a Japanese microbiologist who died of yellow fever in 1928 when making his final efforts to discover the yellow fever pathogen in Accra. NMIMR currently has 9 research departments – Animal Experimentation, Bacteriology, Clinical Pathol-



**Fig. 1.** Noguchi Memorial Institute for Medical Research. It was donated from the Japanese Government in 1979 for research on infectious diseases in Ghana.



**Fig. 2.** Researchers of TMDU are dispatched to Ghana to train young researchers of NMIMR. Technical transfer from Japan to Ghana is one of the activities in the project.

ogy, Electron Microbiology, Epidemiology, Immunology, Nutrition, Parasitology, and Virology. The main institutional scope of research activities is directed at infectious diseases, but research fields are expanding and now, as the disease structure changes in Ghana, include metabolic disorder, hypertension and other diseases.

Since 1979, NMIMR has collaborated with various Japanese institutions on ODA schemes, but our collaboration structure is unique because of its aim and scope. Research collaboration is the main purpose, but the training of young researchers from both Ghana and Japan is being promoted (**Fig. 2**). Two TMDU faculty members are stationed at NMIMR, and research and training have been implemented in collaboration with NMIMR.

Among research collaboration outcomes are important health impacts on Ghanaian residents and some informative for research on infectious diseases in Japan, as detailed below.

### 3. Monitoring Drug Efficacy for HIV Carriers in Ghana

The prevalence of HIV infection among adults is relatively low in Ghana at 1.4% of adult residents in 2012 according to the most recently published data [2]. This is in contrast to much higher rates in southeastern Africa. To keep the situation stable, numerous investigations have been conducted in Ghana from very early stages such as continuous monitoring of HIV infection. HIV sentinel surveys began in Ghana, in fact, in 2000 and medical care for HIV carriers. Antiretroviral therapy (ART) for HIV carriers was first introduced in Ghana in 2003, whereas many other African countries did not do so until 2004-2006. Currently, two alternative drug combination regimens guided by WHO are used (**Table 1**). The WHO guideline was established based on virological information available in Europe and/or North America, however, so it should be examined first for whether on-going ART in Ghana is effective. We also must monitor the appearance of drug-resistant HIV.

For these purposes, we started a cohort study in which we regularly collect samples from HIV-positive donors and monitor parameters such as the number of CD4<sup>+</sup> cells and plasma viral load in the ART time course guided by the government of Ghana. One of the significant achievements in this study was that we have established an in-house quantitative real-time RT-PCR (qRT-PCR) assay for measuring the HIV-1 viral load [3]. In most advanced countries, including Japan, the use of high-grade viral load meters together with expensive commercial kits is nationally standardized or recommended. Nonetheless, many developing countries, including Ghana, cannot afford these for financial reasons. We have thus established in-house qRT-PCR, which requires only less expensive real-time PCR and a labeled probe and primers.

As a result, we have found that ART in operation in Ghana is still effective because over 90% of HIV carriers showed improvement/maintenance of the above parameters, while several cases – 8.2% – showed signs of ART failure even though these victims appear to have taken their drugs regularly and properly (**Table 2**). It must be checked whether failure was due to the appearance of drug-resistant viruses, so we determined genomic sequences for surveying drug-resistant mutations. Referring to the database of HIV-drug-resistant mutations [4], we observed typical drug-resistant mutations in some samples mainly antagonizing toward the effect of AZT/d4T, 3TC, and NVP/EFV.

One of the unique HIV profiles in West-Africa is the presence of HIV-2. Our study detected HIV-2 infection from one of HIV-1 using Western blotting confirmation tests, so another research interest was to determine whether on-going ART in Ghana was effective against HIV-2. We have so far found that 14 patients were positive for HIV-2 infection. Of these 14, only one had single HIV-2 infection and the remaining 13 were positive for dual HIV-1/HIV-2 infection. Although the number of HIV-2-positive individuals enrolled is small, it is likely

**Table 1.** WHO recommended ART Regimens.

Regimen	First choice	Second choice
A	AZT <sup>1</sup> + 3TC <sup>2</sup> + NVP <sup>3</sup>	AZT <sup>1</sup> + 3TC <sup>2</sup> + EFV <sup>4</sup>
B	d4T <sup>5</sup> + 3TC <sup>2</sup> + NVP <sup>3</sup>	d4T <sup>5</sup> + 3TC <sup>2</sup> + EFV <sup>4</sup>

<sup>1</sup>AZT: Zidovudine, <sup>2</sup>3TC: Lamivudine, <sup>3</sup>NVP: Nevirapine, <sup>4</sup>EFV: Efavirenz, <sup>5</sup>d4T: Stavudine

These regimens had been used in Ghana up to the year 2010. Then the guidelines were modified in 2010, in which tenofovir has become available as a second choice drug in the first line drugs and the so-called "second line drugs" comprising of either tenofovir + (emtricitabine or lamivudine) + (lopinavir/r or atazanavir/r) or zidovudine + lamivudine + (lopinavir/r or atazanavir/r) have been added as alternatives [14].

**Table 2.** Efficacy\* of ART for HIV-positive individuals in Ghana in a cohort study from 2011-2013.

Year	2011	2012	2013
Failure	12.8%	17.3%	8.2%
Moderately success	18.4%	14.6%	30.1%
Success	68.8%	68.0%	61.7%

\*Efficacy was evaluated by viral load and CD4 cell number.

that the efficacy of current ART in Ghana for HIV-2 carriers may be comparable to that for HIV-1.

Taken together, the ART regimen currently used in Ghana appears to be effective in the majority of those living with HIV/AIDS. Sequence analyses in the viral reverse transcriptase gene have also shown, however, that typical drug-resistant mutations such as M184V against 3TC and K103N against EFV/NVP are frequently found both among those treated and among treatment-naïve patients [5]. We thus obviously must continue monitoring ART efficacy and HIV-drug-resistant mutations in Ghana.

#### 4. Current Situation of Malaria Drug Selection in Ghana

Malaria is one of the most common infectious diseases in Ghana and is still a "top" killer of children in many sub-Saharan countries [6], especially of those younger than 5 years old. Malaria is vector-borne, transmitted by Anopheline mosquitoes as *Plasmodium* sp., the protozoa that parasitizes in the erythrocytes of mammalian hosts, including humans. Malaria control has many components, with case management one of the most important because no malaria vaccine is yet available.

Antimalarial drugs have been developed to treat the disease, but malaria parasites rapidly develop drug-resistant mutations. Chloroquine (CQ) used to be the drug of choice for malaria, but WHO currently recommends that CQ should not be used to treat falciparum malaria and states that artemisinin-combined therapy (ACT) is the strategy of choice [6]. Biological mechanisms of drug-resistance are not fully understood, however, although genes responsible for resistance to several drugs have been uncovered. Based on current information, the joint Ghana-Japan team analyzed the situation of drug sensitiv-

**Table 3.** Guideline for malaria treatment in Ghana.

Patient category	Recommended therapy
Uncomplicated adult patients	Artesunate + Amodiaquine (AA)
Next choice	Artesunate + Lumefantrine (AL)
Third choice	Dehydroartemisinin + Piperaquine (DHAP)
Uncomplicated pregnant women	1 <sup>st</sup> -2 <sup>nd</sup> trimester: Quinine (Q) 3 <sup>rd</sup> -4 <sup>th</sup> trimester: AQ or AL
Adult Severe malaria	Quinine injection

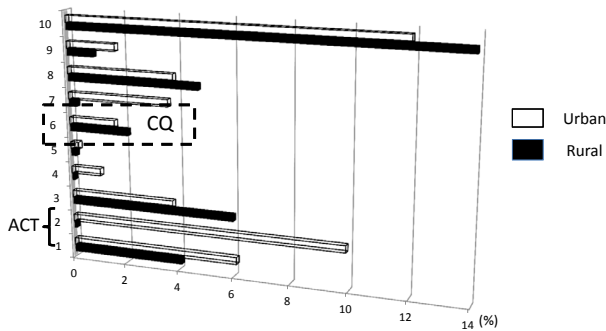
ity to malaria parasites and their gene mutations at gene loci related to drug resistance. At the same time, drug-use for malaria treatment was studied by interviewing medical doctors, pharmacists, nurses, licensed drug sellers, and patients.

We collected blood samples from patients with falciparum malaria, then tested drug sensitivity for CQ, quinine, artesunate (a derivative of artemisinin), and amodiaquin by the standard WHO method (Table 3) [7]. Samples were also subjected to gene-mutation analyses at drug resistance loci. *pfprt* and *pfmd1* were analyzed for CQ resistance. Although drug resistance genes for artemisinin have not yet been identified, SERCA-type *pfATPase6*, considered one of the candidate genes [8, 9], was analyzed for artesunate resistance.

All successfully tested parasite isolates in Ghana were sensitive to artesunate [7]. The *pfATPase6* gene was revealed to be highly polymorphic even in artesunate-sensitive parasites but presumed mutations specific to malaria parasites resistant to artesunate were not observed. Although the physiological roles of polymorphisms in parasites are unclear, it is important to continuously monitor *P. falciparum* susceptibility to artemisinin together with polymorphisms in the *pfATPase6* gene.

CQ resistance in Ghana is unique. ACT was introduced in 2005, and according to new governmental guidelines, CQ ceased being the drug of choice for malaria treatment [9]. Similar political decisions regarding CQ were made in many endemic areas, and many African countries have stopped using CQ. Once CQ use was stopped, however, CQ sensitivity in malaria parasites quickly returned in many areas, including other endemic African areas [10, 11], and we analyzed the situation of CQ sensitivity in malaria parasites in Ghana, expecting a similar situation. Although it was obvious that mutant *pfprt* of *P. falciparum* in Ghana was decreasing in frequency compared to data reported in the past, the proportion of resistant mutations remained around 50%, posing the question of whether CQ was still in use treating malaria in Ghana [12].

In our investigation interviewing medical and nonmedical residents in Ghana, ACT was widely recognized by many medical personnel and they were aware of the importance of not producing drug-resistant malaria para-



**Fig. 3.** Chloroquine is still in use for some malaria patients in Ghana. 1: AS-AQ, 2: AL, 3: DHA, 4: Artesunate, 5: AQ, 6: CQ, 7: Sulfadoxine-Pyrimethamine, 8: Analgesic, 9: Herbal, 10: No idea.



**Fig. 4.** Undergraduate students of TMDU are dispatched to Ghana to have experiences of infectious disease research under the instruction of TMDU and NMIMR researchers.

sites. A matter of concern was the thinking of patients both in urban and rural areas. It was possible to purchase medicines at drug stores without prescription and some still requested CQ for treating malaria (Fig. 3) [12]. Since treatment using a single artemisinin-derivative drug was observed, concerns arose about the emergence of artemisinin-resistant malaria parasites. Results suggest that it is necessary to provide both medical and nonmedical residents with precise ACT-related information more properly for ACT to remain effective in treating malaria in Ghana.

### 5. Vector Research in Ghana

Common infectious diseases in West-Africa include many vector-borne infections such as malaria, viral hemorrhagic fever, and African trypanosomiasis. Vector control is promising in preventing disease transmission, and biological and ecological information is essential for control. Vector research in these years in Ghana revealed several unexpected and new bits of information. (I) From our research on tsetse fly, the vector for African trypanosomiasis, a high frequency of trypanosome-positive samples was observed even in urban Ghana. This suggests that the risk of infection for humans and/or domestic animals is higher than expected in Ghana. (II) WHO recommends that those living in malaria-endemic areas use permethrin-treated bed net for prevention [13]. When we analyzed the situation of knock-down *Anopheles gambiae* resistance in Ghana, most mosquito samples collected in residential Accra had resistance genotypes, suggesting that the effectiveness of permethrin-treated bed nets may be dropping in Ghana. Continuous monitoring of the resistance of *An. gambiae* in Ghana is thus important to understand the effectiveness of insecticide-treated bed-net use. (III) The etiology of viral hemorrhagic fever (VHF) in Ghana is not yet completely understood and it still awaits for further investigation. Among VHF, dengue and yellow fever are transmitted by *Aedes* mosquitoes. However, no detailed surveillance has been made for the distribution and insecticide resistance of *Aedes* mosquitoes in

Ghana. Our nation-wide survey of *Aedes* mosquitoes revealed that the most common species was *Aedes aegypti aegypti* and that *Aedes* mosquitoes were highly resistant to DDT.

### 6. Exchange Activities Between Ghana and Japan

With regular NMIMR-TMDU joint project activities, junior-level NMIMR staff members have been invited to Japan to participate in scientific meetings and to receive technical laboratory training at TMDU. In the last 6 years, over 10 young researchers from NMIMR have stayed at TMDU for laboratory training, and one was promoted to become a regular NMIMR staff member. TMDU accepted PhD students from NMIMR in the hope of more enhanced research collaboration between NMIMR and TMDU. In the last 6 years, one researcher finished and the other is finishing PhD study. TMDU has also sent Medical School undergraduate students to research tropical diseases on site. Since 2010, over 20 TMDU students have stayed at NMIMR and joined our collaboration research projects (Fig. 4). Among these, one student entered graduate school to research malaria. Young researchers and students in both countries are motivated through these activities, and human development in the infectious diseases research field is apparently being achieved.

### 7. Prospects

There is a long history of collaboration between NMIMR and Japanese institutions, and TMDU is currently functioning as a core institution for collaboration with NMIMR. Africa is geographically far from Japan, but Japan has maintained a close relationship with Ghana, especially with NMIMR. It is clear that such an exchange has benefited both Ghana and Japan and therefore more tight relationships are expected in the future. Current re-

search subjects in our project are virology and parasitology, but we intend to widen the scope of research collaboration. As is the case in many developing countries, disease profiles are changing over the long term and noncommunicable diseases are gradually increasing in Ghana. In this sense, basic and clinical research on these diseases must be included in future collaboration. For this, TMDU alone is not enough and we must invite other partner institutions from the Japanese side. This is also an expectation from the Ghanaian side. Consequently, the J-GRID scheme is functioning well at this time and based on the current situation, we are seeking more effective schemes for the future.

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**Name:**  
Eiji Ido

**Affiliation:**  
Professor, Department of Molecular Virology,  
Graduate School of Medical and Dental Sciences,  
Tokyo Medical and Dental University

#### Address:

1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan

#### Brief Career:

1982- Lecturer, Jomo Kenyatta College of Agriculture and Engineering, Kenya (as a member of JOCV)

1984- JICA Medical Expert, Noguchi Memorial Institute for Medical Research, University of Ghana, Ghana

1985- Assistant Professor, Faculty of Mining, Akita University, Japan  
1989- Associate Research Scientist, Oklahoma Medical Research Foundation, USA

1991- Assistant Professor, Institute for Virus Research, Kyoto University, Japan

2010- Professor, Tokyo Medical and Dental University, Japan and Visiting Scientist, Noguchi Memorial Institute for Medical Research, University of Ghana, Ghana

#### Selected Publications:

- "Kinetic studies of human immunodeficiency virus type 1 protease and its active site hydrogen-bond mutant A28S," *J. Biol. Chem.*, Vol.266, pp. 24359-24366, 1991.

- "Ethnic variation of HTLV in the world," *Ethnoepidemiology of Cancer Japan Scientific Societies Press*, Tokyo, Gann Monograph on Cancer Research, Vol.44, pp. 107-120, 1996.

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#### Academic Societies & Scientific Organizations:

- Japanese Society for Virology (JSV)
- Japanese Society for AIDS Research (JSAR)
- Japanese Society of Tropical Medicine (JSTM)
- Japan Association for International Health (JAIH)