Institution: University of Glasgow (UofG)		
Unit of Assessment: UoA12 Engineering		
Title of case study: Origami diagnostic tests enable rapid, low-cost diagnosis of infectious diseases in low- and middle-income countries		
Period when the underpinning research was undertaken: 2016–present		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Jonathan Cooper	Professor, Wolfson Chair of Bioengineering	1991–present
Julien Reboud	Senior Lecturer	2009–present
Period when the claimed impact occurred: 2018–2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Infectious diseases are the leading cause of mortality amongst people in low- and middle-income countries (LMICs). High disease mortality rates are often linked to prohibitive cost and resource obstacles to diagnosis. UofG researchers have developed a unique paper-microfluidic 'origami' diagnostic platform (manufactured by UK SME, Epigem) that uses lateral flow to bring rapid and accurate molecular testing to low-resource under-served rural areas in Uganda and beyond. The device enables DNA analysis, which is normally performed in a laboratory, to be carried out in rural under-served communities more rapidly and accurately than the current gold-standard field-based methods. Both healthcare and policy have changed in Uganda as a result of the devices being used to detect malaria and schistosomiasis, with economic and social impacts for stakeholders/partners.

2. Underpinning research

Research at UofG led by Cooper and Reboud focused on DNA-based point-of-care sensors for infectious agents, as an alternative to conventional immunodiagnostic lateral flow tests. The main advantages of using DNA-based testing are that it differentiates between current and historical infections, whilst simultaneously enabling the highly sensitive identification of the species of pathogens (as is required for informing treatment and care pathways).

Low-cost, integrated, DNA sensors that can test for multiple DNA sequences (as markers of different species of pathogens), were developed at UofG, using hot-wax printing of hydrophobic barriers on paper to define sample and reagent flows [3.1]. The assay can be performed by a non-expert and uniquely involves simple paper-folding (origami) to bring sample and reagents into contact and perform isothermal DNA amplification and detection.

The origami device has been used in a variety of settings to detect the different strains of malaria parasite, schistosomes (a parasitic worm), bacteria (causing sepsis) in humans and sexually transmitted infections in animals. All of these represent a challenge for traditional detection methods which cannot be implemented in the field and are more costly.

Existing techniques have been unable to provide the integration of the assay steps into a single, easy-to-use platform. The devices designed at UofG uniquely use origami-folding to generate purified DNA from raw samples (e.g. blood), and further perform amplification and detection of multiple DNA types at once. The results can be simply recorded and analysed using a cloud-based platform.

Using over GBP1.5 million of funding from the EPSRC under the '*Novel low-cost diagnostic tools and their impact in Africa*' grant [3.2], and in partnership with Ugandan Ministry of Health, UofG researchers worked with healthcare technicians to validate the strip-based sensor, analogous to a pregnancy test, to generate easy-to-visualise readouts. The goal of this work was to deliver health and economic sustainability in the Global South by enabling low-cost, effective and

accurate diagnosis of infectious diseases, namely malaria and schistosomiasis. The unique format of the device used in this work enabled the diagnosis of different diseases with just one test device (e.g. different species of schistosomiasis and malaria, both from finger-prick blood).

Published results show that the specificity of the origami platform exceeds that of the current immunodiagnostics and commercial loop-mediated isothermal amplification (LAMP) methods [3.1, 3.3]. A unique, key advantage of the origami platform exists in its ability to have high specificity; it can differentiate between closely related malarial parasites *P. falciparum* and *P. vivax* infections [3.1, 3.3]. Making such distinctions is challenging, time-consuming and costly for current laboratory-based diagnostic methods. However, it is easily carried out in the field using the origami technique, guiding malarial treatment (e.g. *P. falciparum* is more likely to progress to a severe illness, while *P. vivax* requires a different therapeutics to eliminate dormant forms).

Following initial testing of the malaria origami sensors at the UK's Malaria Reference Laboratory [3.1], in-field testing of the origami malaria sensors was led by Cooper in Uganda [3.4] with grant funding from EPSRC [3.5]. The origami technique allowed non-expert technicians and healthcare workers from the Ugandan Ministry of Health to diagnose individuals using the simple appearance of coloured lines to indicate a positive result.

The DNA-based origami platform produced results that were 92.8% accurate (compared with the gold-standard PCR DNA detection methods, which cannot be implemented in the field), while it outcompetes established field-based techniques in malaria detection of immunodiagnostics (82% accuracy) and microscopy (86% accuracy) [3.4]. Collectively these findings illustrate key points about the origami platform: it is easy to use, fast and reliable and has a high sensitivity [3.1–3.5].

3. References to the research

3.1. Xu, G., Nolder, D., Reboud, J., Oguike, M. C., van Schalkwyk, D. A., Sutherland, C. J., & Cooper, J. M., 2016.Paper-Origami-Based Multiplexed Malaria Diagnostics from Whole Blood. Angewandte Chemie International Edition, 55(49): pp. 15250–15253. doi:10.1002/anie.201606060 *

3.2. Grant Funding: Professor J. Cooper. Novel low-cost diagnostic tools and their impact in Africa. EPSRC. 01/02/2018–31/01/2021. GBP1,585,505.

3.3. Xu, G., Nolder, D., Reboud, J., Oguike, M.C., Sutherland, C.J. and Cooper, J., 2018. Origami-based Multiplexed Infectious Disease Diagnostics from Whole Blood - Research Data., University of Glasgow. doi:10.5525/gla.researchdata.339

3.4. Reboud, J., Xu, G., Garrett, A., Adriko, M., Yang, Z., Tukahebwa, E.M., Rowell, C. and Cooper, J.M., 2019. Paper-based microfluidics for DNA diagnostics of malaria in low resource underserved rural communities. Proceedings of the National Academy of Sciences, 116(11); pp.4834–4842. doi:10.1073/pnas.1812296116 *

3.5. Yang, Z., Xu, G., Reboud, J., Ali, S.A., Kaur, G., McGiven, J., Boby, N., Gupta, P.K., Chaudhuri, P. and Cooper, J.M., 2018. Rapid veterinary diagnosis of bovine reproductive infectious diseases from semen using paper-origami DNA microfluidics. ACS sensors, 3(2); pp.403–409. doi: 10.1021/acssensors.7b00825 [Available on request from HEI]

*=best indicators of quality

4. Details of the impact

Malaria and other infectious diseases remain a global health priority. Low-cost rapid diagnostic tests (RDTs) can help determine the prevalence of infectious diseases in LMICs, informing treatment and care pathways in community settings (without access to diagnostic laboratories). The origami-fold paper-based device underpinned by UofG research addresses an urgent emerging challenge noted with regard to RDTs concerning the accuracy of the tests. The combination of nucleic acid testing with lateral flow detection and origami-style folds represents a game-changing innovation in low-cost RDTs that responds to the need for high detection

accuracy, indicating whether an infection is current and enabling simultaneous testing of multiple infectious diseases in field settings.

Impacts on health

The Glasgow research has underpinned the following health impacts to date:

- The new, low-cost diagnostic technology is easier to use, more rapid and more accurate than current diagnostics, and has been trialled and adopted in the Tororo, Mayuge and Apac regions of Uganda (which ranks 3rd in the world for malaria cases);
- Informed by field trials revealing higher than expected levels of schistosomiasis, the Tororo health authority and the Ugandan Ministry of Health implemented a decision to carry out mass drug adminstrations of schoolchildren.

As a result of the device created at UofG and its impact in Tororo, Uganda, a new Ugandan public health initiative has been created. This initiative is a clear enhancement of disease prevention and has changed understanding and policy among national and regional healthcare and education authorities with regard to disease control [5.1-5.3].

The origami testing platform has directly generated health impacts for school children in Uganda, as it was used in 'field trials' – testing trials carried out a local school. These trials identified a previously unidentified, high-level of schistosomiasis infection, resulting in a mass drug administration that benefitted 940 children in the first instance.

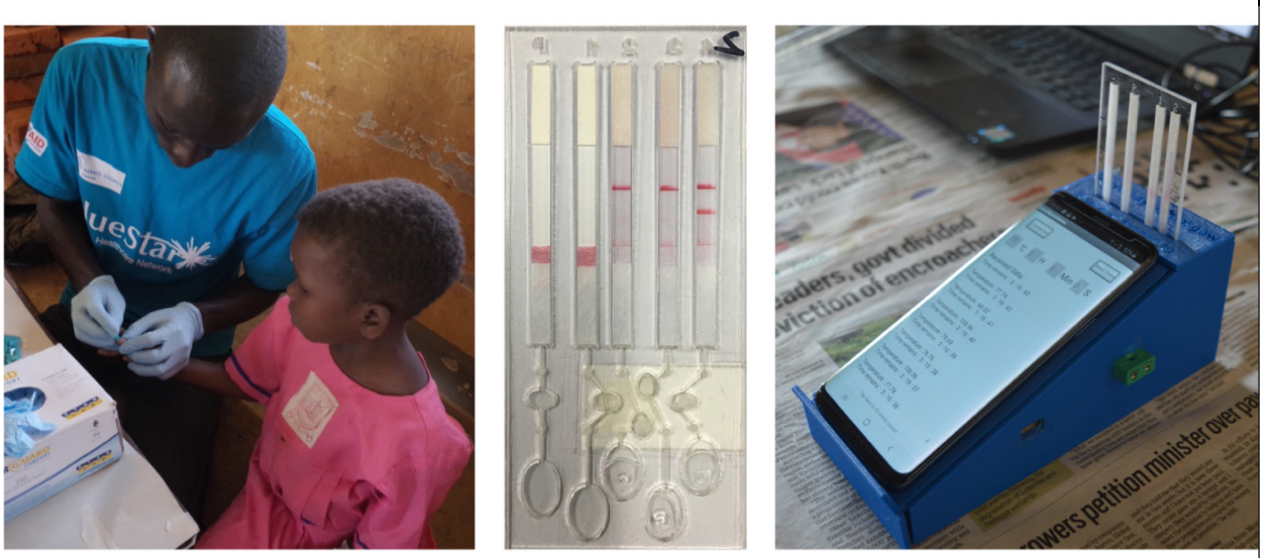

Image collage showing (left) an individual having a blood sample taken which will be analysed; (middle), the sample-to-answer multiplexed cartridge involving a paper-based microfluidic test, enabling DNA based species-specific detection at the point-of-need and (right) the use of a mobile phone-controlled platform (with the cartridge inserted), enabling computing with a cloud-based decision support tool to record the result.

The platform identified malarial and schistosomiasis infection levels in remote regions of Uganda faster and with higher accuracy than current conventional field-based methods. This was demonstrated clearly in 2018–2019 field trials (led by Cooper in collaboration with the Tororo District and Ministry of Health) carried out in primary schools in Uganda's Tororo District. The device consistently and correctly detected higher levels of infections in the schoolchildren which had been under-estimated or undetected by the health authorities. The District's Chief Administrative Officer stated [5.1] that the prevalence of schistosomiasis in particular surprised the authorities there, and *'based on this evidence Tororo District has…put in place a programme of mass drug administration to address the widespread problem.'* As a direct result of UofG's findings in Uganda, an initial 940 children (from one school alone) were included in the first tranche of schistosomiasis treatment in 2019, carried out by the Ministry of Health. UofG were invited to expand the Tororo District school testing programme that they commenced in July

2019, and returned in 2020, with the District confirming that the work had *'spearhead[ed] the promotion of new point-of-care DNA based diagnostics for infectious diseases in other districts in Uganda'* [5.1]. This is confirmed in a subsequent letter stating that the UofG *'testing…has helped accelerate the Ministry of Health Mass Drug Administration (MDA) in the region'* [5.2].

Impacts on commerce and the economy

Uniquely combining DNA analysis multiplexed testing that is faster and more accurate than the conventional RDTs offers opportunities to industrial partners. To date, this has achieved the following impacts:

- Within Epigem Ltd, where new commercial opportunities have arisen for this UK SME, (the main source of their growing revenue comes from collaboration with Prof Cooper) and collaboration with UofG has allowed the company to meet its objectives [5.4]
- Contributing to innovation and entrepreneurial activity in the Ugandan Industrial Research Institute (UIRI) on the design and delivery of new products or services [5.5];
- Within Mologic Ltd, where the technology is being adapted for the detection of SARS-CoV-2 in an industrial collaboration with the MRC (MR/V035401/1, 2021) [5.6].

Using a prototype tested in a trial with UK's Malaria Reference Laboratory, manufacturer Epigem undertook to *'design and manufacture cartridges to house all the components, to increase usability and, consequently, application in remote situations'* [5.4]. Epigem's engineers *'created a manufacturable design in plastic, to accommodate the paper lateral flow device, giving it the robust structural integrity needed for testing in rural environments.'* Epigem also *'provided devices for use in field trials in Uganda. Epigem consider the devices to be mass manufacturable at low cost.'*

In 2020, Epigem supported Uganda Industrial Research Institute (UIRI) − a center of excellence for Industrial Research in the East African Community − to develop local modes of mass manufacturing and are working through the African Network for Drugs and Diagnostics Innovation to develop a manufacturing facility to produce the diagnostic devices in Africa [5.5]. "*We have been working with Professor Cooper's team for more than 3 years which led to a close partnership resourced by Global Challenge Research Funding and UKRI grants (EP/T029765/1) to explore the manufacturing of mobile health technologies for clinical diagnostics of infectious diseases, based upon DNA analysis. In 2019 we signed a joint Memorandum of Agreement to focus our future activities on co-development of mobile health within an open-innovation framework. This relationship has also enabled us to interact with UK SMEs including Epigem Ltd and Mologic Ltd, exploring routes for local manufacture of diagnostic devices and opening up new opportunities for these companies in Uganda."* – Executive Director of UIRI [5.5]

UIRI is now *"translating methods to make the diagnostic cartridges, originally manufactured by computer numerical control (CNC) machining at Epigem Ltd, to be produced in Kampala – providing a low cost, low volume technique for the initial trials. [UIRI] are keen to continue to work with Epigem to translate the design into mass manufacturable, lower-cost versions, that can be used by teams working in Mulago Hospital Infectious Disease Institute and the Ministry of Health, Uganda in their disease screening activities as well as by the Veterinary Diagnostic Unit at Makerere University in supporting animal health through testing livestock*." – Executive Director of UIRI [5.5]

UofG researchers most recently are collaborating with Mologic on translating the device for use, exploiting the origami technique to measure infections as a "respiratory panel" of SARS-CoV-2, RSV and influenza; funding was secured in late 2020 [5.6]. Mologic is a leading developer of lateral flow and rapid diagnostic technologies and will work closely in partnership with The Gates Foundation and UK Aid to develop, validate and manufacture the new product/platform through a social enterprise spin-out called Global Access Diagnostics (without shareholders and delinked from commercial return to provide rapid responses to global pandemics) [5.6]. The technologies are now being produced in the UK and in Senegal [5.6], and the collaboration's progression unpderins a philosophy that is closely aligned with the Glasgow team's ambition.

5. Sources to corroborate the impact

5.1. Letter 04 July 2019: Chief Administrative Officer, Tororo District, Local Government, Uganda, confirming that testing had revealed unforeseen levels of infection and underpinned their decision to administer schistosomiasis treatment to 940 schoolchildren in one school.
5.2. Letter 26 February 2020: Chief Administrative Officer, Tororo District, Local Government, Uganda, confirming that UofG testing had helped accelerate Ugandan Ministry of Health's mass drug administration in the region.
5.3. Letter 27 February 2020: Chief Administrative Officer, Tororo District, Local Government, Uganda, inviting UofG to expand the ongoing schistosomiasis (bilharzia) testing programme.
5.4. Letter 08 February 2021: Company Director, Epigem, confirming participation in field trials and expansion of work to partner with Ugandan Industrial Research Institute on local modes of manufacturing.
5.5. Letter 10 February 2021: Uganda Industrial Research Institute (UIRI) letter
5.6. Letter 03 February 2021: Chief Scientific Officer, Mologic Inc letter