Institution: Royal Veterinary College (RVC)

Unit of Assessment: A 6 Agriculture, Veterinary and Food Science

Title of case study: Elucidating the transmission dynamics of novel zoonotic schistosomiasis to inform avenues for sustainable control in Africa

Period when the underpinning research was undertaken: 01/10/2014 – 31/12/2020

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:
Joanne Webster	Professor of Parasitic Diseases	01/10/2014 – present
Martin Walker	Lecturer in Epidemiology	01/02/2017 – present

Period when the claimed impact occurred: 01/10/2014 – 31/12/2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact (indicative maximum 100 words)

Schistosomiasis, a neglected tropical disease (NTD) of profound importance, affects over 240,000,000 of the poorest people and untold millions of their livestock. RVC research has revealed the emergence and establishment of human:animal zoonotic schistosomes, exacerbated by human activities. Together with academic, governmental and industrial partners, RVC researchers have used this understanding to drive more effective approaches to control, including increased awareness, policy change and better diagnostics and treatment to improve both human and animal health across the developing world.

2. Underpinning research (indicative maximum 500 words)

Professor Webster was recruited from Imperial College in 2014 to lead the RVC's strategy to study pathogen flow between wildlife, livestock and people. Her research into schistosomiasis, in close collaboration with partners within disease-endemic countries, exemplifies this strategy of interdisciplinary research to address global issues affecting human and animal health. Seminal analysis and modelling work undertaken 2018-2019 led by Webster in collaboration with RVC co-investigator, Walker, and colleagues at Imperial, published in the *New England Journal of Medicine,* systematically assessed the progress made by the current schistosomiasis control programmes in 9 countries across sub-Saharan Africa (SSA) and the Middle East [1]. This clearly demonstrated the need to re-evaluate progress and treatment strategies in national schistosomiasis control programmes more frequently, taking local epidemiologic data into consideration, to determine treatment effect and appropriate resource allocations. The research also indicated biological and operational factors that can lead to infection persistence in some settings, most notably evident by ongoing high levels of infection with intestinal schistosomiasis caused by *S. mansoni* in East Africa (Uganda and Tanzania) and urogenital schistosomiasis, assumed to be caused by *S. haematobium*, in West Africa (Niger, Mali and Senegal) [1].

The greatest concern for any mass drug administration (MDA) programme is the risk of drug resistance emerging, which is particularly pertinent for schistosomiasis as there is only a single effective drug, praziquantel, available globally. Webster, in collaboration with colleagues at Imperial and the Sanger Institute, analysed data on *S. mansoni* in Uganda and demonstrated, through incorporation of improved analytical measures, that reductions in drug efficacy were detected amongst infected school-aged children in settings under the longest drug selection pressures [2]. Furthermore, of key importance, Webster and her partners' work demonstrated the complexity of the epidemiology of human schistosomiasis and how the role of animals in this cannot be ignored. *S. haematobium*, the causative agent of human urogenital schistosomiasis, has classically been assumed to be an exclusively human pathogen – and hence, so long as drug resistance does not establish, sufficient coverage of MDA should be enough to interrupt transmission. However, Webster's *Lancet Planetary Health* study collected data between 2016-2018 that showed that in areas of West Africa where human schistosomiasis has proved difficult to control (with up to 88% ongoing infection prevalence and morbidities due to schistosomiasis amongst children and adults, despite high coverage control efforts for almost 20 years), human schistosomes had hybridised with schistosome species found in livestock to produce viable

hybrids that perpetuate and expand transmission [3]. This is one of several publications she led, convincingly demonstrating that a One Health approach is needed to eliminate schistosomiasis from a number of different areas of the world.

The group's work across Africa and Asia has also shown that human schistosomes can infect and sustain transmission through wild rodent reservoirs, which given the inherently difficult challenges in terms of controlling rodents globally, provides another ultimate challenge to achieving interruption of schistosomiasis transmission. Between May 2016 and August 2018, local wildlife populations in West Africa were found to be reservoirs of human (*S. mansoni*), livestock (*S. bovis*) and zoonotic hybrid *Schistosoma spp.* combinations (*S. haematobium* with both *S. bovis* and *S. mansoni*) [4]. Notably, phylogenetic analyses demonstrated that it was the same parasite genotypes circulating in rodents, humans and snail intermediate hosts, indicative of shared ongoing transmission [5]. Furthermore, metanalyses performed upon available data from Asia showed that, whilst multi-sectoral control efforts across China have been successful in reducing *S. japonicum* in humans and livestock, infection prevalence has been maintained, particularly in hilly/mountainous habitats, increasing in the sympatric rodent populations, thereby accounting for ongoing transmission and recrudescence in these areas [6].

These studies have demonstrated the role of animals, both livestock and wildlife in the complex epidemiology of schistosomiasis which needs to be considered in any global control programme. Furthermore, RVC research has documented that livestock schistosomiasis can perpetuate the poverty cycle of the poorest subsistence farmers, through high levels of animal mortality and morbidity [7]. Social surveys revealed a widespread demand for (and use/misuse of) praziquantel in livestock. Praziquantel tablets, donated by the World Health Organisation (WHO) MDA programmes for school-aged children, were frequently then administered to infected livestock, with little knowledge of application or dosage requirements [7]. Inappropriate MDA of anthelmintics to livestock raises risk of praziquantel-resistance and is particularly pertinent for schistosomiasis, as this is the only efficacious drug for both humans and livestock.

3. References to the research (indicative maximum of six references)

1. Deol AK, Fleming FM, ***Calvo-Urbano B***, **Walker M**, Bucumi V, Gnandou I, Tukahebwa EM, Jemu S, Mwingira UJ, Alkohlani A, Traoré M, Ruberanziza E, Touré S, Basáñez MG, French MD, **Webster JP**. (2019) Schistosomiasis - Assessing Progress toward the 2020 and 2025 Global Goals. *New England Journal of Medicine.* 381(26):2519-2528. https://doi.org/10.1056/NEJMoa1812165

2. Crellen T, Walker M, Lamberton PH, Kabatereine NB, Tukahebwa EM, Cotton JA, **Webster JP**. (2016) Reduced Efficacy of Praziquantel Against Schistosoma mansoni Is Associated With Multiple Rounds of Mass Drug Administration. *Clinical Infectious Diseases.* 63(9):1151-1159. https://doi.org/10.1093/cid/ciw506

3. ***Léger E, Borlase A***, Fall CB, Diouf ND, Diop SD, ***Yasenev L***, ***Catalano S***, Thiam CT, Ndiaye A, Emery A, ***Morrell A***, Rabone M, Ndao M, Faye B, Rollinson D, Rudge JW, Sène M, **Webster JP.** (2020) Prevalence and distribution of schistosomiasis in human, livestock, and snail populations in northern Senegal: a One Health epidemiological study of a multi-host system. *Lancet Planetary Health*. 4(8), e330–e342. https://doi.org/10.1016/S2542-5196(20)30129-7

4. ***Catalano S***, Sène M, Diouf ND, Fall CB, ***Borlase A***, ***Léger E***, Bâ K, **Webster JP**. (2018) Rodents as Natural Hosts of Zoonotic *Schistosoma* Species and Hybrids: An Epidemiological and Evolutionary Perspective From West Africa. *Journal of Infectious Diseases.* 218(3):429–433. https://doi.org/10.1093/infdis/jiy029

5. ***Catalano S***, ***Léger E***, Fall CB, ***Borlase A***, Diop SD, Berger D, Webster BL, Faye B, Diouf ND, Rollinson D, Sène M, Bâ K, **Webster JP**. (2020) Multihost Transmission of *Schistosoma mansoni in* Senegal, 2015-2018. *Emerging Infectious Diseases.* 26(6):1234-1242. https://doi.org/10.3201/eid2606.200107

6. Zou, H-Y, Yu, Q-F, Qui, C., **Webster, J.P**. & Lu, D-B. (2020) Meta-analyses of *Schistosoma japonicum* infections in wild rodents across China over time indicates a potential challenge to the 2030 elimination targets *PLoS Neglected Tropical Diseases*. 14(9):e0008652. https://doi.org/10.1371/journal.pntd.0008652

7. ***Gower CM, Vince L***, **Webster JP**. (2017) Should we be treating animal schistosomiasis in Africa? The need for a One-Health economic evaluation of schistosomiasis burden and control in

sub-Saharan Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene.* 111(6):244–247. https://doi.org/10.1093/trstmh/trx047

Other Quality Indicators

References 3-5 and 7 were funded by Biotechnology and Biological Sciences Research Council (BBSRC) Zoonoses and Emerging Livestock Systems (ZELS) programme grants, which were awarded to Professor Webster as PI and held at the RVC. In addition, Webster has been supported by a Bill & Melinda Gates foundation grant (SCORE) in partnership with (funding received via) University of Georgia. She has obtained peer-reviewed quality research funding GBP1,320,055 since joining the RVC in 2014. This work has also been supported by impact accelerator grants and connecting capabilities funding awarded to the RVC and allocated to Webster's group based on the quality of her work and its potential for impact (GBP320,174). Furthermore, Webster has continued to attract funding for her work on Schistosomiasis. She is a work programme lead on the UKRI-Global Challenges Research Fund: RCUK Collective Fund Action Against Child Stunting Hub and manages a budget of GBP947,726 (2019-2024) and on the European and Developing Countries Clinical Trials partnership, 'FibroSchot', receiving GBP657,711 (2018-2022) for the work package she leads.

Webster has been an Executive Board Member of the Schistosomiasis Control Initiative (SCI) and WHO Global Working Group on Monitoring of Drug Efficacy since 2014. She has served on the WHO Expert Panel Working Group: NTD Elimination Strategies since 2017, and as Expert Advisor and Head of Praziquantel Working Group, the WHO Schistosomiasis Guideline Development Group, and WHO Open Access Data Platform Group since 2018. In 2019, Webster joined the BBSRC Strategic Funding Expert Panel Review Board, is an Expert Advisor for The Wellcome Trust: Innovations for Impact Review Board, and is part of the WHO Technical Working Group: Protocols to Verify Interruption of Transmission of Schistosomiasis.

Webster was BBSRC Innovator of the Year Finalist for International Impact (2018) and listed as 1 of 5 Inspirational Women shaping the future of International Development by the London International Development Centre for International Women's Day 2019. Webster has provided invited keynote/plenary/guest lectures on this research globally, including presenting at the House of Lords and the House of Commons (UK). [Text removed for publication]

Reference 1 was published with an editorial and invited follow-up 'Letter to Editor': Deol A, French MD, & Webster JP (2020) Schistosomiasis and the Global Goals. *New England Journal of Medicine* 382 (16): 1576. Reference 2 was 'Editor's Choice'. Reference 4 is in the top 1% for its field, based on the field weighted citation indices and references 1, 2 and 7 are in the top 5%.

4. Details of the impact (indicative maximum 750 words)

Schistosomiasis is 2nd only to malaria in terms of socio-economic impact from parasitic disease, infecting approximately 240,000,000 people, 90% of which reside within SSA (WHO, 2020). Through research and advocacy, Webster's team's work has helped raise global awareness of schistosomiasis in humans and animals, creating widespread demand for affordable treatment, realising significant benefits to millions of people and livestock. Her seminal findings have led to WHO recommending a verification framework involving diagnosis in animals be undertaken, facilitating disease elimination via moving towards a One Health approach in the following ways:

1. Changes in awareness and influences of international policy for the control of zoonotic schistosomiasis in SSA

National and international policy has historically underestimated, or ignored, both the risk to continued high levels of human schistosomiasis through zoonotic hybridization events and the direct impact of livestock schistosomiasis in relation to livelihoods and economic productivity, particularly across Africa. Improved understanding is now being used to inform public health measures locally, nationally and internationally, resulting in improved practices to control zoonotic and animal schistosomiasis. The WHO set ambitious targets for control of morbidity (by 2020), elimination as a public health problem (by 2025), and interruption of transmission of schistosomiasis within selected countries of SSA (by 2025, and 2030 for China), through MDA to children or communities with praziquantel. However, the approach to achieve this vision focused only on human disease. For the first time, due to Webster's empirical research, elucidation of the role of zoonotic schistosomiasis in maintaining transmission in Africa and Asia has been

recognised and a need for revised control incorporating the role of animal hosts and hybrid schistosomes have been stated in WHO policy [a, b, c]. The WHO Guidelines for Control and Elimination of Schistosomiasis, finalised in 2020 and due to be published in the first quarter of 2021, recommend (Recommendation 6) that in communities near to the interruption of transmission (defined as having no autochthonous human cases reported for 5 years), a verification framework incorporating testing of animals (livestock and wildlife) be undertaken, using improved diagnostic tests of high specificity and sensitivity [a, b]. A new WHO NTD Roadmap 2030 was officially approved 12 November 2020, which states *'Treatment of animals, keeping animals out of transmission sites'* as a Strategic Intervention and *'Understand zoonotic transmission'* in the Assessment of Actions Required to Meet 2030 Target - both recommendations informed by RVC research [a, c]. RVC research also highlighted the need to apply WASH principles to help control interspecies transmission, which was included in the WHO Guidelines on Sanitation and Health (published in 2018), as treatment of humans alone will not interrupt transmission where animal reservoirs exist [a, d]. Webster's work also alerted the WHO to the possibility of potential praziquantel resistance emerging under areas under the longest drug selective pressures and highlighted the need for integrated monitoring of drug efficacy. Based in part on Webster's advocacy around this issue, WHO guidelines propose that 10% of the funding provided for control programs is to be allocated to monitoring and evaluation activities, including that for the potential emergence and/or establishment of praziquantel resistance [a, b].

2. Improved treatment for animals via more appropriate veterinary-formula drugs

RVC research revealed an unmet demand for veterinary-formula praziquantel, which had led to inappropriate use of human drug in livestock. Subsequently, RVC researchers began working with WHO, Merck-KGA, and SCI, to maximise access to a veterinary-formula praziquantel. Livestock owners have reported that access to appropriate drugs and dosage information was their most significant limiting factor for successful control of animal schistosomiasis [e]. Within West Africa, until late 2017, the only available veterinary-formula praziquantel product was combined with levamisole [Text removed for publication], for tapeworm treatment [e]. However, the labelled dosage is ineffective against schistosomes and levamisole toxicity limits higher dosage. As a result of RVC's study, a new livestock formula [Text removed for publication], which is appropriate for treating schistosomiasis [Text removed for publication], has been made available in West Africa that field veterinarians in the areas covered by the project are using routinely to treat Schistosomiasis [e].

3. Improved capacity and expertise to diagnose/monitor disease in humans and animals

RVC's academic work in Niger and Senegal has created local capacities, upskilling and equipping human and veterinary health professionals to diagnose human and livestock schistosomiasis. For example, ultrasonography is the diagnostic tool of choice for detecting pathologic conditions associated with human schistosomiasis, both in hospital and field-based settings. It is non-invasive and well accepted by communities, but there was originally no expertise nor facilities available within Senegal. RVC researchers arranged for a young clinician to travel to Niger for intensive competency training and purchased and imported a portable ultrasound for the Senegalese team. Transfer of skills through the ZELS research/clinical activities across Senegal has enabled further clinicians to become fully proficient in schistosomiasis-related ultrasonography to assess early and late stage morbidity profiles and undertake research to understand the differences in pathologies resulting from hybrid vs. non-hybrid infections [f].

4. Modified attitudes and practice of those at threat from schistosomiasis

This understanding of the transmission of hybrid schistosome species revealed previously unappreciated risks and points the way to control interventions. At grass-roots in Senegal and Niger, information posters and colouring books have been produced and supplied to local school children and families, raising awareness of schistosomiasis and potential for zoonotic transmission [g]. English and French versions of colouring books covering schistosomiasis (including symptoms, impact, treatment and prevention) were developed together with partners in Senegal and Niger, with >400 books distributed to rural communities since August 2019 [g]. Unlike previous similar initiatives, this new edition included both human and animal schistosomiasis. RVC researchers also drew from their recent papers to provide grass roots/teen open access articles available in English and French via www.sciencejournalsforkids.org, which have been downloaded >1200 times in total since March 2019 [g]. Local information workshops were delivered, using local dialect translators,

with key stakeholders, including subsistence farmers, veterinary technicians and practitioners [h]. RVC researchers have demonstrated a difference in terms of local knowledge, attitudes and practices in these stakeholders between areas where they are working and where they are not [h]. In Linguere and Richard Toll, where Webster's group carried out educational activities, community members involved in focus group discussions were able to describe the signs of schistosomiasis associated with infected animals and knew that schistosomiasis could be transmitted from animals to humans. They knew that they could get infected by sick cattle, drinking water from ponds where the animals drink, living among infected cattle and consuming meat/milk from infected animals [h].

5. Creation of Bio-bank materials and Open Access Database to facilitate future research

The RVC contributes content to the Wellcome funded Schistosomiasis collection (SCAN) at the Natural History Museum (NHM), to both provide and receive specimens for research purposes, and a new Infectious Disease Data Observatory (IDDO) schistosomiasis and soil-transmitted helminthiases platform has been set up to catalogue drug efficacy epidemiological data [i]. RVC projects have contributed to the SCAN sample bank, which has archived larval human and veterinary schistosomes and led to new projects and collaborations, a particular strength being to provide the link between state-of-the-art genomics centres and fieldwork teams in developing countries [j]. All RVC schistosome collections made in collaboration with the NHM have been archived at SCAN, constituting 20% of the current collection, opening possibilities for their future use and widening the benefits of the sampling programme. SCAN collections include approximately 475,000 larval schistosomes, 73,000 Mollusca, and 14,000 DNA extractions, and specimen lots numbering 3,900 for schistosomes and 4,900 for Mollusca for legacy collections. Since 2016, 14 organisations have been provided with material for research purposes and 32 papers have been published using material provided from this programme of research [j].

5. Sources to corroborate the impact (indicative maximum of 10 references)

All corroborating evidence has been uploaded with the submission.

a. Letter from WHO corroborating the impact of RVC research on the new WHO guidelines recommending that in communities nearing interruption of transmission, testing of livestock and wildlife be undertaken, and consideration of the role of animal hosts in control and elimination.
b. Draft WHO Guidelines for Control and Elimination of Schistosomiasis, plus email from WHO confirming as finalised version.
c. WHO Ending the Neglect to Attain the Sustainable Development Goals: A Roadmap for NTDs 2021-2030, endorsed in November 2020 https://www.who.int/publications/i/item/9789240010352
d. WHO Guidelines of Sanitation and Health citing RVC research https://apps.who.int/iris/bitstream/handle/10665/274939/9789241514705-eng.pdf?ua=1
e. Letter and email from Universite Gaston Berger corroborating availability of new combined formulation of praziquantel and levamisole suitable for treating schistosomiasis in livestock [Text removed for publication]
f. Letter from University Cheikh Anta Diop of Dakar Faculty of Medicine corroborating improved capacity and expertise to diagnose/monitor disease
g. Information posters [in French] and colouring books [in English and French] distributed in West Africa as educational tools https://www.rvc.ac.uk/Media/Default/Research/documents/rvc-bilharzia-colouring-book-english.pdf and https://www.rvc.ac.uk/Media/Default/Research/documents/rvc-bilharzia-colouring-book-french.pdf plus teen articles [in English and French] https://sciencejournalforkids.org/wp-content/uploads/2019/09/rodents_article.pdf and https://sciencejournalforkids.org/wp-content/uploads/2019/09/rodents-article-fr.pdf, plus email from publisher corroborating article downloads.
h. Letter from IDS corroborating knowledge, attitudes and practices of livestock owners
i. IDDO website corroborating schistosomiasis platform launch, where Walker is scientific lead: https://www.iddo.org/news/schistosomiasis-and-sths-platform-launched
j. Letter and email from Natural History Museum corroborating SCAN biobank collections & use: https://www.nhm.ac.uk/our-science/our-work/sustainability/schistosomiasis-collection.html