

# Chapter 5

## Case Studies: Challenge Studies in Low- and Middle-Income Countries



This review identified 13 case studies involving primary publications detailing HCS in 5 LMICs published from 1992–2018:

- (i) 4 enteric pathogen HCS in Thailand with cholera (Suntharasamai et al. 1992; Pitisuttithum et al. 2002) and *Shigella* (Bodhidatta et al. 2012; Pitisuttithum et al. 2016),
- (ii) 5 falciparum malaria HCS in Sub-Saharan Africa in Tanzania (Shekalaghe et al. 2014; Jongo et al. 2018), Kenya (Hodgson et al. 2014), and Gabon (Lell et al. 2017; Dejon-Agobe et al. 2018), and
- (iii) 4 vivax malaria HCS in Colombia (Herrera et al. 2009; Herrera et al. 2011; Arévalo-Herrera et al. 2014; Vallejo et al. 2016).

These endemic-region HCS together recruited approximately 400 participants—which, as mentioned earlier, amounts to less than 1% of the >40,000 human volunteers who have participated in HCS worldwide (i.e., >99% of HCS participants have been in HICs) since World War II (Evers et al. 2015; Kalil et al. 2012). While other LMIC HCS may have taken place during this period of time (e.g., unpublished studies and/or those not captured in the detailed case studies below), the authors who estimated that 40,000 individuals have participated in HCS overall suggested that this total would be an underestimate—meaning that LMIC participants have in any case been grossly under-represented (Evers et al. 2015). This suggests that endemic-region HCS has been a neglected area of research, even though the vast majority of infectious disease morbidity and mortality occurs in endemic LMICs. In addition to the above studies, HCS are currently being considered and/or conducted in LMICs including Equatorial Guinea, Gabon, India, Indonesia, Kenya, Malawi, Mali, Tanzania, Thailand, Uganda, and Vietnam (Personal communications from study participants) (Baay et al. 2018).

Although these 13 published studies all took place within endemic countries that have active transmission of the pathogen in question in at least part of the country, they frequently took place in a city/location where there was no local transmission (e.g., the studies in Kenya and Colombia were in non-endemic areas). We discuss the ethical salience of decisions regarding the location of study sites below.

These 13 studies from 1992 to 2018 were increasingly pre-registered (in line with general trends for clinical research (Ioannidis 2015)). Pre-registration is arguably ethically important since it can help to (i) improve transparency (e.g., by requiring analyses and methods to be specified in advance rather than altered once the trial is in progress), (ii) reduce publication bias (e.g., by providing an incentive for publication of all research findings, whether favourable or not), (iii) reduce unnecessary duplication of research efforts (thus reducing the chance that participants will be exposed to challenge infections unnecessarily) and (iv) increase standardisation and/or comparability across similar research programs (if research groups are able to co-ordinate) which may serve to increase the accuracy and impact of results (Ioannidis 2015). As one interviewee argued:

[It's important that] the results are disseminated very widely, whatever the results are, which is a major issue that we have across all of research ... you're putting these individuals at more risk than in some clinical research, it makes it get an even greater imperative to disseminate the results, totally transparently. [Scientist, UK/Europe]

## 5.1 Cholera and *Shigella* Challenge Studies in Thailand

We identified 4 studies of diarrhoeal disease using HCS designs in Thailand, all using models developed in previous (non-endemic) North American studies. These comprised 2 HCS that aimed to replicate infection models of cholera (*Vibrio cholerae*) developed in the US (Suntharasamai et al. 1992; Pitisuttithum et al. 2002); and 2 HCS using *Shigella sonnei* (a major cause of bacterial dysentery), first to develop an infection model (Bodhidatta et al. 2012) and subsequently to test a live attenuated vaccine using this model (Pitisuttithum et al. 2016) (See Table 5.1).

### 5.1.1 Rationale and Review Process

The cholera HCS conducted at Mahidol Univeristy, Bangkok, Thailand, published by Suntharasamai et al. (1992) is, to our knowledge, the first endemic-region LMIC HCS since 1956 (see history section above) (Suntharasamai et al. 1992) and was followed by a similar HCS by the same group with a different cholera serotype in 2002 (Pitisuttithum et al. 2002). The stated rationale for the two cholera studies was to replicate previous cholera HCS studies (in non-endemic populations) because “ethnic factors, gut flora, and immunological background” could lead to important differences in the response to cholera infection in the (endemic) Thai population (Suntharasamai et al. 1992; Pitisuttithum et al. 2002). It was thus intended to (i) investigate hypotheses regarding host-pathogen interactions in semi-immune individuals (which would be infeasible in a non-endemic setting), (ii) develop models of infection in an endemic population against which interventions

**Table 5.1** Cholera and *Shigella* HCS in Thailand

Pathogen	Cholera (el Tor)	Cholera (O139)	<i>Shigella sonnei</i>	<i>Shigella sonnei</i>
Year of publication	1992	2002	2012	2016
First author	Suntharasamai	Pitisuttithum	Bodhidatta	Pitisuttithum
Country	Thailand	Thailand	Thailand	Thailand
Consent	Test of understanding	Test of understanding	Test of understanding	Test of understanding
Follow-up after study	N/S	N/S	N/S	2 months
Mode of challenge	Oral	Oral	Oral	Oral
Source of challenge strain	Laboratory strain	Laboratory strain	Laboratory strain	Laboratory strain
Diagnosis/treatment initiation	Symptoms plus cultures	Symptoms plus cultures	Symptoms plus cultures	Symptoms plus cultures
Treatment	Antibiotics, IV/oral fluids for diarrhoea			
Clinical attack rate	90%	100%	75%	20% (controls)
Severe symptoms	Nil	Yes, Up to 16L diarrhoea	Yes, severe dysentery in 3 (8.3%)	1 (16%) severe dysentery in control
Other burdens	Dysentery, isolation	Dysentery, isolation	Dysentery, isolation	Dysentery, isolation
Reduced severity in endemic population	Yes	Yes	N/S	Unclear; less shedding of vaccine strain
In- or outpatient	Inpatient	Inpatient	Inpatient	Inpatient
Third party risks/mitigation	Released once stool cultures negative			
Long-term effects	N/S	N/S	N/S	N/S
Pathogen	Cholera (el Tor)	Cholera (O139)	<i>Shigella sonnei</i>	<i>Shigella sonnei</i>
Year of publication	1992	2001	2012	2016
First author surname	Suntharasamai	Pitisuttithum	Bodhidatta	Pitisuttithum
Country	Thailand	Thailand	Thailand	Thailand
Location (endemic or not)	Bangkok (endemic)	Bangkok (endemic)	Bangkok (endemic)	Bangkok (endemic)
International Collaborators	Nil	USA, WHO	USA	USA
Prior HIC HCS	Yes	Yes	Yes	Yes
Pre-registration	N/S	N/S	N/S	<a href="https://ClinicalTrials.gov">ClinicalTrials.gov</a>

(continued)

**Table 5.1** (continued)

Pathogen	Cholera (el Tor)	Cholera (O139)	<i>Shigella sonnei</i>	<i>Shigella sonnei</i>
Year of publication	1992	2001	2012	2016
First author surname	Suntharasamai	Pitisuttithum	Bodhidatta	Pitisuttithum
Country	Thailand	Thailand	Thailand	Thailand
Community engagement	N/S	N/S	N/S	N/S
Ethics/IRB	Local review	Local review	Local review	Local review, US Army IRB
Challenge strain regulation	N/S	N/S	N/S	FDA CGMP (vaccine)
Rationale	Model development	Model development	Model development	Vaccine trial
n	26	35	36	20 (6 controls)
% female	0%	31.43%	36.11%	N/S
Participants' background	N/S	85% labourers, unemployed, students	N/S	N/S

*N/S* not specified, *IV* Intravenous, *WHO* World Health Organisation, *HLA-B27* a genetic marker of the risk of post-infectious arthritis

'International collaborators' were derived from institutional affiliation of authors only

could be tested, and (iii) respond to local disease burden priorities. The models developed were intended for use in future local cholera vaccine trials, although no subsequent vaccine trials have cited these studies thus far.

The stated rationales for the *Shigella* studies were more detailed. In addition to assessing different response to challenge in a Thai population, the authors noted (i) the large global burden of *Shigella* (including among Thai children) related to acute disease and its long-term complications (post-infectious bowel symptoms, arthritis), (ii) increasing drug resistance of *Shigella*, and (iii) the lack of an animal model (because humans are the only natural host of the pathogen). The model was developed in the 2012 *Shigella* HCS and subsequently used in 2016 to test a vaccine. The studies were reviewed and approved by the local institutional ethics committee, the Ministry of Public Health (Thailand), and, in the case of the *Shigella* studies, the U.S. Army Human Subjects Research Review Board. The vaccine used in the 2016 study was produced according to US FDA cGMP and presumably approved for research use by the Thai FDA. The challenge strains used were not governed by specific Thai regulation. The 2016 trial was the first of the Thai studies to be pre-registered on [clinicaltrials.gov](http://clinicaltrials.gov).

### **5.1.2 Recruitment, Participant Selection, Consent, and Payment**

One of the four studies reported the background of participants: 43% students, 37% labourers, and 20% unemployed (Pitisuttithum et al. 2002). Participants were recruited from a population in which the diseases are endemic, although not all participants had evidence of high levels of past exposure (for example, in the 2012 *Shigella* study 20% of those screened had antibodies to *Shigella*) (Bodhidatta et al. 2012). Exclusion criteria included (i) in all studies: general co-morbidities and pregnancy (due to potential increased risks), (ii) in the *Shigella* studies: carrying HLA-B27 (due to the associated risk of post-infectious arthritis) (iii) in the vaccine trial: those with abnormal bowel habit (which might reduce the risk of post-infectious irritable bowel syndrome and/or improve the clarity of vaccine efficacy estimates). Cholera severity is known to vary with blood type, thus the cholera studies recruited individuals with a variety of blood types in order to increase generalisability of findings. Participants also underwent psychological screening by investigators to select those who would tolerate inpatient isolation. All Thai HCS involved a written test of comprehension as part of the informed consent process. Payment is not recorded in the publications, but was apparently indexed to local wages for unskilled labour and the period of isolation in the inpatient unit (Personal communications from interview participants).

### **5.1.3 Burdens (Including Risks to Participants and Third Parties)**

If required, symptomatic participants (e.g., those with diarrhoea and/or dysentery) received oral or intravenous rehydration. Among subjects who became symptomatic, there were few severe symptoms, although stool volumes in the cholera studies ranged from around half a litre to up to 16 litres. On average, symptoms were milder than in similar studies in non-endemic North American populations, suggesting that enteric pathogen HCS may at least sometimes be less burdensome in an endemic population.

Post-infectious complications, including irritable bowel syndrome, reactive arthritis, and Guillain-Barre syndrome, have been observed after *Shigella* infection (Thabane et al. 2007; Hannu 2011; Ajene et al. 2013) but they are rare and have not been reported to occur among HCS participants. The probability of such complications can be difficult to predict in the absence of known risk factors. Reactive arthritis has the known risk factor of HLA-B27 (a genetic marker) (Hannu 2011); thus those with this marker were excluded to avoid excessive risks—although even those who do not carry HLA-B27 have a small risk of post-infectious arthritis and other complications. Scientists interviewed for this study were not aware of any long-term complications related to study participation.

The studies were conducted in fully inpatient settings with strict biosafety procedures, decontamination of effluent, and treatment of participants (with proof of cure) to reduce third-party risks. In the *Shigella* trial, among those vaccinated 56% were found to shed the vaccine strain in stool, which could potentially spread to others, although no cases of transmission were reported in a previous Israeli study of this vaccine (Orr et al. 2005).<sup>1</sup>

### 5.1.4 Summary and Outcomes

The Thai Cholera HCS were noteworthy in the sense that they demonstrated that such studies could be successfully and safely conducted in an endemic LMIC. The model was able to demonstrate differences in symptomatic disease in an endemic population, but it has not yet been used to test novel interventions for cholera. The *Shigella* model was relatively quickly advanced to a vaccine trial, however the latter was not able to provide accurate estimates of vaccine efficacy because the attack rate among controls (given placebo) was 20% (i.e., a failure to replicate the attack rate of 75% in the HCS in which the model was developed (Bodhidatta et al. 2012))—since so few of those who were not vaccinated developed disease, the estimate of vaccine efficacy (i.e., equal to any further reduction in risk of disease post-challenge in vaccines) was not statistically significant. We have been informed that Thai researchers are considering undertaking more HCS in the future (Personal communications from study participants).

## 5.2 Falciparum Malaria Challenge Studies in Africa

We identified 5 Sub-Saharan African HCS involving falciparum malaria in Tanzania, Kenya, and Gabon (Hodgson et al. 2014; Shekalaghe et al. 2014; Lell et al. 2017; Dejon-Agobe et al. 2018; Jongco et al. 2018). These studies are part of an international research program using cryopreserved *P. falciparum* (Pf) sporozoites from a laboratory strain (NF54) known to be sensitive to chloroquine and produced in increasingly controlled laboratory settings since the 1980s (Chulay et al. 1986). The research program began at the US Walter Reed Army Institute of Research (WRAIR) and is now led by a US private company, Sanaria Inc., in collaboration with several research centres worldwide. This laboratory strain has been tested in multiple studies (in both HICs and LMICs) where it has been used as (i) a human challenge agent (non-attenuated) and (ii) a vaccine candidate (radiation attenuated), administered either by injection (intradermal, intramuscular, or

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<sup>1</sup>Oral live attenuated vaccines, such as the oral polio vaccine, can immunise others in the community when spread via the stool of those vaccinated.

intravenous) or by mosquito bite (Lyke et al. 2010; Hodgson et al. 2014; Shekalaghe et al. 2014; Gómez-Pérez et al. 2015; Olotu et al. 2018).

The US FDA-approved NF54 challenge strain is produced according to cGMP regulations designed to ensure purity (only the sporozoite form of malaria parasites, only one strain) and asepsis (not containing bacterial or other pathogens). After multiple models and trials in non-endemic-regions, this research group, with international collaborators, has more recently been conducting endemic-region falciparum malaria HCS, resulting in the sub-Saharan African publications reviewed below (See also Table 5.2). One advantage of this model is that it does not require mosquitoes to administer the infection challenge (which is instead injected by needle) thus obviating the need for high biosafety level insectaries (which are rare in LMICs and involve significant costs) and/or the need to import mosquitoes (which might involve risks to the local population, as discussed in Sect. 3.4) (Billingsley et al. 2014); whether malaria HCS by needle is generalisable to wild-type infection by mosquito bite is unknown, but the model uses sporozoites (i.e., the same form of malaria parasite involved in transmission from mosquitoes to humans) in order to investigate the early stages of malaria infection (and, for example, whether these can be prevented or reduced by novel interventions).

### 5.2.1 *Rationale and Review Process*

This program of sub-Saharan African HCS research, conducted in conjunction with HIC collaborators, was designed to (i) test hypotheses regarding host-pathogen interactions in malaria-endemic and/or semi-immune populations (that would have been infeasible in HIC HCS) as well as those with genetic traits thought to affect malaria infection (e.g. sickle cell and  $\alpha$ -thalassaemia), (ii) develop models of infection in an endemic population against which to test interventions (thus aiming to improve the generalisability of malaria HCS to African populations), (iii) test malaria interventions (e.g. vaccines) against these models, (iv) respond to local disease burden priorities, and (v) further develop local capacity for infectious disease research (at well-established African institutions in all three countries with significant pre-existing research expertise). Four of the five studies were focused on investigating host-pathogen interactions and/or developing Africa-specific infection models as translations of models that had previously been conducted in non-endemic HICs. The fifth study used the locally-tested model to trial a malaria vaccine candidate (GMZ2) against challenge (Dejon-Agobe et al. 2018).

All five studies were pre-registered (with US [clinicaltrials.gov](http://clinicaltrials.gov) and/or the Pan-African Clinical Trials registry). Ethics committees at the African institutions and collaborating HIC institutions reviewed the studies, which were also reviewed by national committees in the African countries. The challenge strain had prior regulatory approval by the US FDA, and was reviewed by Kenyan, Tanzanian, and Gabonese regulators. The studies took place at three research institutes with longstanding African-HIC collaborative international research programs.

**Table 5.2** Falciparum malaria HCS in Africa

Pathogen	Malaria (falciparum)	Malaria (falciparum)	Malaria (falciparum)	Malaria (falciparum)	Malaria (falciparum)	Malaria (falciparum)
Year of publication	2014	2014	2018	2018	2018	2018
First author	Hodgson	Shekalaghe	Jongo	Lell	Dejon-Agobe	Dejon-Agobe
Country	Kenya	Tanzania	Tanzania	Gabon	Gabon	Gabon
Location (endemic or not)	Nairobi (non-endemic)	Bagamoyo (endemic)	Bagamoyo (endemic)	Lambaréné (endemic)	Lambaréné (endemic)	Lambaréné (endemic)
Type of study	Infection model	Infection model	Vaccine trial	Infection model	Infection model	Vaccine trial
International collaborators	UK, USA	Netherlands, Switzerland, USA	Switzerland, USA	Germany, USA	Germany, USA	Germany, Netherlands, USA
Prior HIC HCS	Yes	Yes	Yes	Yes	Yes	Yes
Pre-registration	Pan African clinical trial registry	<a href="http://Clinicaltrials.gov">Clinicaltrials.gov</a>	<a href="http://Clinicaltrials.gov">Clinicaltrials.gov</a>	<a href="http://Clinicaltrials.gov">Clinicaltrials.gov</a>	<a href="http://Clinicaltrials.gov">Clinicaltrials.gov</a>	Pan African clinical trial registry
Community engagement	Yes—extensive publication of process	N/S	N/S	N/S	N/S	N/S
Ethics/IRB	Local, national, and international review	Local, national, and international review	Local, national, and international review	Local, national, and international review	Local, national, and international review	Local, national, and international review
Challenge strain regulation	Kenyan Pharmacy and Poisons Board, US FDA	Tanzania FDA, US FDA	Tanzania FDA, US FDA	Direction Médicament et de la Pharmacie, US FDA	Direction Médicament et de la Pharmacie, US FDA	Direction Médicament et de la Pharmacie, US FDA
Rationale	Model development	Model development	Vaccine trial	Model development	Vaccine trial	Vaccine trial
n	28	30 (6 controls)	67 (18 controls)	25	50 (10 controls)	50 (10 controls)
% female	39.29%	0%	0%	48%	0%	0%
Recruitment details	54% student, 17% unemployed, 29% other	Students at higher learning institutions	Students at higher learning institutions	N/S	N/S	N/S
Pathogen	Malaria (falciparum)	Malaria (falciparum)	Malaria (falciparum)	Malaria (falciparum)	Malaria (falciparum)	Malaria (falciparum)
Year of publication	2014	2014	2018	2018	2018	2018
First author surname	Hodgson	Shekalaghe	Jongo	Lell	Dejon-Agobe	Dejon-Agobe
Country	Kenya	Tanzania	Tanzania	Gabon	Gabon	Gabon
Consent	Test of understanding, time for consideration	Test of understanding, time for consideration	Test of understanding, time for consideration	Test of understanding, time for consideration	Test of understanding, time for consideration	Test of understanding, time for consideration

(continued)

**Table 5.2** (continued)

Pathogen	Malaria (falciparum)	Malaria (falciparum)	Malaria (falciparum)	Malaria (falciparum)	Malaria (falciparum)
Year of publication	2014	2014	2018	2018	2018
First author surname	Hodgson	Shekalaghe	Jongo	Lell	Dejon-Agobe
Country	Kenya	Tanzania	Tanzania	Gabon	Gabon
Follow-up post-challenge	Exit questionnaire	Up to 168 days for recurrent malaria; 1 infection during follow-up (not challenge strain)	N/S	Up to 3 months for recurrent malaria	8 weeks
Mode of challenge	Intramuscular	Intradermal	Intravenous	Intravenous	Intravenous
Pathogen strain	NF54 Lab. strain	NF54 Lab. strain	NF54 Lab. strain	NF54 Lab. strain	NF54 Lab. strain
Diagnosis	Symptoms + microscopy	Symptoms + microscopy	Symptoms + microscopy	Symptoms + microscopy OR qPCR	Symptoms + microscopy
Treatment	Antimalarial	Antimalarial	Antimalarial	Antimalarial (pre- and post-)	Antimalarial (pre- and post-)
Clinical attack rate	100%	75%	39% (controls)	Europeans (100%), Sickle cell Gabonese (14%), Other Gabonese (67%)	44% (overall)
Severe symptoms n (%)	17 (61%)	1 (3%)	3 (4.5%)—all fever only	Europeans: 3 (60%), Gabonese: 0 (0%)	Nil
Other burdens	Inpatient isolation, monitoring	Inpatient isolation, monitoring	Inpatient isolation, monitoring	Monitoring	Monitoring
Reduced severity in endemic population	N/S	Yes	Yes	Yes	Yes
In- or outpatient	Inpatient	Partly outpatient	Inpatient post-challenge (12 days)	Outpatient	Outpatient

N/S Not Specified, *ICH* International Conference on Harmonisation, *MoH* Ministry of Health, *AEs* Adverse Effects  
 ‘International collaborators’ were derived from institutional affiliation of authors only

The Kenyan group published ethics committee and regulatory approval times (local Kenyan committee: 6 months; collaborating UK university committee: 2 months; Kenyan Pharmacy and Poisons Board: 3 weeks) (Hodgson et al. 2015). Since the timeliness (as well as thoroughness) of ethical review can itself be ethically important (e.g., because undue delays of beneficial research arguably delay benefits of new interventions for the eventual target population), more standardised reporting of review times across multiple studies might be called for.

### ***5.2.2 Recruitment, Participant Selection, Consent, and Payment***

The Kenyan study was conducted in Nairobi, a non-endemic part of the country and the investigators found it difficult to recruit as many semi- and/or highly-immune individuals as they had planned, largely because of a lack of exposure to prior infection in the local population in Nairobi (the research group have since begun conducting HCS in and/or recruiting from more endemic parts of Kenya (Kapulu et al. 2018)). In contrast, the Tanzanian and Gabonese studies took place in endemic areas and were able to recruit semi-immune individuals (and/or those with innate resistance to malaria) more easily. All studies aimed to recruit healthy, non-pregnant, African adults who would share at least some characteristics (e.g., similarities in genetic factors, microbiome, etc.) with high priority target populations for falciparum malaria interventions (e.g., African children). In addition, the studies (to varying degrees) aimed to recruit individuals with acquired immunity (from past malaria infection) in order to study relationships between immunity and response to challenge; the study in Gabon by Lell et al. also recruited a small group of local expatriate Europeans in order to make direct comparisons between European and Gabonese HCS outcomes (Lell et al. 2017).

In order to reduce risks to participants, all five studies excluded those who were pregnant or intending to become pregnant and those with various medically significant comorbidities and/or particular co-infections (e.g., HIV, viral hepatitis). In terms of comorbidities, exclusion criteria included having certain risk factors for cardiac events (based on previous data of cardiac events during malaria HCS (Nieman et al. 2009; van Meer et al. 2014), see Sect. 3.3.5) and psychiatric risk factors (see Sect. 3.3.6.1) (Dejon-Agobe et al. 2018). Investigators in this program had initially planned to exclude individuals with  $\alpha$ -thalassaemia trait (because this trait may provide some innate resistance to malaria infection leading to concerns that this could affect HCS results); but they ultimately included these individuals when the high frequency of the trait in the local population became apparent because of the need to avoid (potentially unfair) exclusion of such individuals in future vaccine trials.

Consent in all cases involved a test of understanding. Some studies aimed to recruit relatively well-educated individuals, with a particular focus in the Kenyan

study on recruiting medical students, because it was expected that such individuals would be more able to understand the study and thus provide adequately informed consent (Hodgson et al. 2014; Shekalaghe et al. 2014; Hodgson et al. 2015). Although the Kenyan study only conducted information sessions for prospective participants with medical students (from whom the majority of the study population was expected to be recruited), the final study population was mixed (54% students, 17% unemployed, 29% other); the authors concluded that “there was no clear advantage to exclusively targeting medical students and future studies would appeal to students of all disciplines.” (Hodgson et al. 2015). Given that non-students and unemployed individuals were also able to pass a test of understanding as part of the consent process, these findings might also support the recruitment of (a larger proportion of) the general adult population in future studies. In Tanzania, all participants were drawn from higher learning institutions, and 100% were male (reflecting lower local rates of higher education among females in general (Kilango et al. 2017)).

The Kenyan group published payment amounts in an article highlighting “lessons learnt” from their first HCS. Participants were paid around \$50 USD per overnight stay, as well as smaller amounts for clinic visits and travel costs, amounting to total payments of around \$250-\$500 USD (Hodgson et al. 2015; Nordling 2018). Payment levels were carefully considered by both local and UK ethics committees, which judged that decided amounts would “neither unduly coerce potential participants nor set a difficult precedent for other research conducted within the programme” (Hodgson et al. 2015; Njue et al. 2018). Payment did, however, lead to short-lived controversy in the local media (Gathura 2018; Kenya Medical Research Institute (KEMRI) 2018). In response to media coverage, the local research institution issued a Statement that included details of the study (including the study rationale, the reasons for inpatient monitoring, the minimisation of risks to participants, and the prior approval by relevant ethical review bodies) and information regarding determinations of the level of payment. The Statement notes that “[T]he participants were compensated for the time they spent at the in-patient facility. The amount compensated was arrived at by considering what they would earn on a daily basis were they engaged in their daily earning activities.” (Kenya Medical Research Institute (KEMRI) 2018).

As a comparison, the HCS in Gabon paid participants similar amounts indexed to local wages (personal communication, expert stakeholder), although the Gabonese study was an outpatient design and payment figures have not been published; in any case payment has not led to controversy in that setting. One Kenyan researcher interviewed for this project indicated that, despite the media controversy, local researchers felt that the level of payment was appropriate—although the group did consider a series of smaller payments rather than one large payment at the end of the study:

[Payment has] been controversial, I think, because of the amount that ended up being given. And it's not so much the daily amount than the lump sum amount – and because it ended up being quite a substantial figure, if you add it up. But if this was being given on a daily basis probably during the study [it wouldn't have seemed] that high ... What changed? Might we

have reconsidered given the [controversy in the media]? I think we still feel that rate was fair, in our context. And I don't think there were any plans to lower it, because it wouldn't make sense if you consider the fact that [it was based on national] minimum wage ... for casual labour ... probably what might ever been considered is ... whether to give it as a lump sum or give it periodically instead of building up into a nice packet at the end of the day. I can see participants will want a lump sum, because then they can do something practical. But, we fear that [this large amount] was again being seen ... people focus on the lump sum amount more than what the participants need. [Scientist involved in the Kenyan HCS]

### 5.2.3 *Burdens (Including Risks to Participants and Third Parties)*

The rate of severe malaria symptoms was generally lower in African individuals (with the exception of the Kenyan study, discussed below), especially those with innate or acquired immunity, than in previous HIC falciparum malaria HCS. In this sense these endemic LMIC malaria HCS presented relatively lower risks to participants than HIC HCS. Arguably, the use of more sensitive diagnostic methods (e.g., PCR) could have reduced risks in terms of symptoms still further, and perhaps helped to support the case for outpatient studies. For example, in some previous HIC malaria HCS, if a participant had symptoms without malaria parasites on blood microscopy, investigators had access to quantitative polymerase chain reaction (qPCR) testing for malaria (a more sensitive test than microscopy) and initiated treatment if this was positive (Sheehy et al. 2013). Timely qPCR was not locally available in these African studies (although samples were tested using such methods at a later date for research purposes). In any case, treatment was effective and no participant experienced treatment failure or recurrent (study-related) malaria during the follow-up period.

A large proportion (61%) of Kenyan participants ultimately developed at least one severe symptom of malaria—a rate similar to European participants, perhaps in part due to the non-endemic setting in Nairobi—but none required hospital care. In contrast, the rate of severe symptoms was much lower among Tanzanian and Gabonese participants (see Table 5.2), potentially because they were drawn from more endemic populations (and thus had greater immunity).

The Gabonese studies took place in an endemic area and predominantly involved outpatient design. Likewise, the Tanzanian studies took place in an endemic area and used a mixed out- and inpatient design. The Kenyan study conducted in Nairobi (a non-endemic area) employed inpatient design partly because traffic-related delays could prevent timely access to medical care and partly because investigators were being especially cautious as this was the first HCS performed in Kenya. One member of the research team described decisions related to the design of the study as follows:

I would have been happy to do the Kenyan study as an outpatient setting [but] the traffic was a massive issue ... [And especially because this] was a pilot study, [the] first one in the country. [People] said, 'There will be a lot of anxiety about this' ... [T]he idea was that we

would need to [have close inpatient monitoring] to provide reassurance [to] the ethical bodies ... but, you know, it was terrifying, actually, when you're travelling to and from the setting, because the traffic was such that if there was an ambulance coming through, the traffic was so gridlocked, you couldn't actually physically get an ambulance along any of the roads. [Scientist involved in the Kenyan HCS]

In terms of risk to third parties, universal treatment upon diagnosis and/or at the end of the study period and the short duration of challenge infection reduced risks significantly. Duration of malaria infection affects third-party risk because gametocytes, the transmissible form of malaria, take 7–15 days to develop (Roberts et al. 2013)—meaning that risks to third parties increase with time since infection. The Kenyan study posed the lowest risk of transmission (effectively zero risk), both because it was an inpatient study and because of a lack of mosquito vectors in Nairobi. In the 2014 Tanzania study, participants were kept as inpatients for 21 days and any who had not been diagnosed with malaria by this time were discharged and continued to participate as outpatients until day 28, at which time they were treated regardless of whether they met the diagnostic threshold. There was a (perhaps very) low probability of transmission of malaria in such circumstances (Karl et al. 2011; Roberts et al. 2013) (and this could, in future, be quantified by qPCR measurement of gametocyte levels during study participation). The Gabon study was conducted on a largely outpatient basis and likewise may have involved a low probability of transmission from study participants to the wider community, in the context of a high local background malaria transmission.

#### 5.2.4 *Summary and Outcomes*

Among these studies were two significant milestones for LMIC HCS research: the first HCS in Africa since the 1950s (Allison 1954; Bearcroft 1956; Shekalaghe et al. 2014), and the first HCS involving vaccine efficacy testing in Africa (Dejon-Agobe et al. 2018). In terms of scientific outcomes, the research program has clarified the protective effects of acquired immunity (which led to a delay to onset of parasitaemia), sickle cell trait (which was shown to be associated with lower levels of symptomatic malaria), and  $\alpha$ -thalassaemia (which was less protective than anticipated), which might support the recruitment of such groups to future vaccine efficacy trials.

Authors of the Kenyan study noted that one participant had (qPCR positive, microscopy negative) asymptomatic parasitaemia (which was successfully treated) at the end of the study, and that future (endemic region) studies of longer duration could investigate the transmissibility of such asymptomatic infections in partially immune individuals (see also Vallejo et al. 2016). However, they also note that this would entail ethical trade-offs involving difficult choices between (i) long periods of inpatient isolation for participants or (ii) potential risks of transmission to third parties where an outpatient model is used and there are local mosquito vectors.

The Kenyan group published an extensive account of “lessons learnt” during and after this HCS. Such lessons included (i) the importance of prospective multi-stakeholder engagement and listening to the concerns of the local community, (ii) the need for extensive information sessions for participants to ensure that they were able to understand the study, (iii) the need to include local sub-populations (e.g. those with haemoglobinopathies) so that they would not be unfairly excluded from the benefits of HCS research, (iv) the need for longer duration studies of naturally-acquired immunity (since semi-immune participants took longer to develop an infection after challenge) and models of transmissibility, and (v) the importance of support from other centres with prior experience conducting malaria HCS in helping to ensure the safety and efficiency of the Kenyan study (Hodgson et al. 2015), Researchers at the same institution have also subsequently published social science work related to malaria HCS (Njue et al. 2018). The publication of such insights from experience with HCS, as well as the integration of biological and social science work related to HCS, could be considered a model of best practice in terms of engagement and the sharing of ethically relevant practical details that might inform future HCS designs.

### **5.3 Vivax Malaria Challenge Studies in Colombia**

The 4 published vivax malaria HCS in Colombia, beginning in 2009 (the earliest malaria HCS in an endemic country that we identified apart from the historical cases discussed above—See Sect. 2.5) were conducted by a well-established research group in Cali (a non-endemic city with endemic areas of transmission relatively nearby—within a few hours’ drive). The local institution has been involved in malaria research for many decades, including, for example, maintaining a longstanding malaria vector mosquito insectary, which provided the mosquitoes for these studies. The HCS formed part of a local research program, one of the goals of which is the development of vivax malaria interventions, especially vaccines.

Since there is no available laboratory strain of vivax malaria, the endemic country setting of the institution enabled researchers to obtain wild-type malaria parasites from consenting patient donors infected in nearby endemic parts of the country (immediately prior to these patients receiving treatment), transport these parasites to Cali, infect insectary-reared mosquitoes (after careful screening for other blood-borne infections), and challenge HCS participants.

#### ***5.3.1 Rationale and Review Process***

This research program, led by local researchers (in some cases in collaboration with international scientists), was designed to (i) investigate hypotheses regarding host-pathogen interactions, including in semi-immune individuals (i.e. study designs that are only feasible in a study centre in/near an endemic setting), (ii) develop a

model of infection against which to test interventions, (iii) test novel interventions (e.g. a vivax malaria vaccine), (iv) respond to local disease burden and maximise generalisability by using local wild-type parasites, and (v) ensure minimisation of third-party risks by conducting HCS in a non-endemic area of Colombia with no local vector mosquitoes (only laboratory mosquitoes were used under strict biosafety precautions). The research program began by testing a new vivax HCS model in malaria naïve individuals in 2009 (Herrera et al. 2009). This model was later refined in 2011 (Herrera et al. 2011), tested in semi-immune individuals in 2014 (Arévalo-Herrera et al. 2014), and ultimately used to test a vaccine in 2016 (Arévalo-Herrera et al. 2016). From 2014, the studies were pre-registered on [clinicaltrials.gov](http://clinicaltrials.gov).

The studies were reviewed and approved by local institutional ethics committees and, where there was significant US collaboration, by US committees at collaborating institutions. The first study was also reviewed by WHO. Challenge organisms are not governed by specific Colombian regulations; interviewed scientists with knowledge of the studies described significant efforts that were made to ensure that the laboratory environment (including insectary-mosquitoes) and the challenge material were as close to FDA-style GMP as possible (including extensive screening of donor blood), noting that full compliance with stringent GMP requirements (such as those used for the NF54 lab strain in the African studies above) would not be possible in the absence of a laboratory strain of vivax.

One regulatory issue that affected the group was applying for insurance (e.g., for research-related harm to participants). Local Colombian insurers (backed by international, usually North American, reinsurers) were initially reluctant to cover the research, which created a delay of approximately two years, as described by a member of the research team:

[Insurers didn't] want to provide the insurance ... they are thinking that maybe ... we are not designing the [study] protocol [well], or that the volunteers are at high risk of [problems related to] safety. So, to convince them, it was very difficult for us ... For the first clinical trial, the phase one ... it took us like two years [to get] that insurance ... [Since we got it, and they know us] we [have been able to] renew our insurance without problems. [Myriam Arévalo-Herrera, scientist, Colombia]

The researchers have never had to make a claim against this insurance (since no lasting harms have occurred among volunteers), however this experience highlighted an additional practical issue that may sometimes be more difficult in LMICs than HICs (Table 5.3).

### ***5.3.2 Recruitment, Participant Selection, Consent, and Payment***

The studies recruited healthy adults from the general population with a focus on malaria-naïve and/or semi-immune volunteers depending on the research question. The authors note the ethically relevant point that, because new interventions for

**Table 5.3** Vivax malaria challenge studies in Colombia

Pathogen	Malaria (vivax)	Malaria (vivax)	Malaria (vivax)	Malaria (vivax)
Year of publication	2009	2011	2014	2016
First author surname	Herrera	Herrera	Arévalo-Herrera	Arévalo-Herrera
Country	Colombia	Colombia	Colombia	Colombia
Location (endemic or not)	Cali (no vectors)	Cali (no vectors)	Cali (no vectors)	Cali (no vectors)
Pre-registration	N/S	N/S	<a href="http://Clinicaltrials.gov">Clinicaltrials.gov</a>	<a href="http://Clinicaltrials.gov">Clinicaltrials.gov</a>
Type of study	Infection model	Infection model	Infection model, test of acquired immunity	Vaccine trial
International collaborators	Brazil, USA, WHO	Brazil, USA	Brazil	USA
Prior HIC HCS	No	No	No	No
Community engagement	N/S	N/S	N/S	N/S
Ethics/IRB	Local and international review	Local and international review	Local review	Local review
Challenge strain regulation	N/A	N/A	N/A	N/A
Rationale	Model development	Model development	Model development	Vaccine trial
n	18	22 (5 controls)	16	28
% female	50%	52.9%	37.5%	64%
Recruitment	Malaria-naïve	Malaria-naïve	Malaria-naïve and semi-immune	Malaria-naïve
Pathogen	Malaria (vivax)	Malaria (vivax)	Malaria (vivax)	Malaria (vivax)
Year of publication	2009	2011	2014	2016
First author surname	Herrera	Herrera	Arévalo-Herrera	Arévalo-Herrera
Country	Colombia	Colombia	Colombia	Colombia
Consent	Multiple information sessions, standard consent	Multiple information sessions, standard consent	Test of understanding	Test of understanding
Follow-up post-challenge	18 months	1 year	3 months	2 months

(continued)

**Table 5.3** (continued)

Pathogen	Malaria (vivax)	Malaria (vivax)	Malaria (vivax)	Malaria (vivax)
Year of publication	2009	2011	2014	2016
First author surname	Herrera	Herrera	Arévalo-Herrera	Arévalo-Herrera
Country	Colombia	Colombia	Colombia	Colombia
Mode of challenge	Mosquito + donor blood	Mosquito + donor blood	Mosquito + donor blood	Mosquito + donor blood
Pathogen strain	Wild type	Wild type	Wild type	Wild type
Diagnosis/treatment initiation	Microscopy	Microscopy + retrospective qPCR	Microscopy + qPCR	Microscopy + qPCR
Treatment	Antimalarial plus primaquine	Antimalarial plus primaquine	Antimalarial plus primaquine	Antimalarial plus primaquine
Clinical attack rate	94%	100%	100% in malaria naïve, 33% in semi-immune	7% in vaccines, 71% in infectivity controls (duffy negative)
Mild-moderate symptoms	Symptoms of malaria	Symptoms of malaria	Symptoms of malaria	N/S
Severe symptoms	Nil	1 (anxiety crisis)	Some with severe malaria symptoms	N/S
Reduced severity in endemic population	N/A	N/S	Yes	N/A
In- or outpatient	Outpatient	Outpatient	Outpatient (except semi-immune individuals)	Outpatient
Long-term effects	N/S	N/S	N/S	N/S

N/S Not Specified, *ICH* International Conference on Harmonisation, *FDA* US Food and Drug Administration

'International collaborators' were derived from institutional affiliation of authors only

malaria (e.g., vaccines) will potentially be used in semi-immune individuals, such individuals should arguably be included in at least some HCS research (an argument also made in support of the recruitment practices of African malaria HCS discussed above). Exclusion criteria were predominantly designed to reduce risks (e.g., G6PD deficiency—a risk factor for adverse effects with primaquine treatment of vivax, HIV and other major co-infections, and pregnancy).

The consent process allowed time for consideration across multiple sessions, and prospective participants were encouraged to discuss their participation with family members. A written test of understanding was used from 2011 onwards. The authors emphasise that participants could withdraw from the studies at any time. This did sometimes occur before challenge, but there were no withdrawals after challenge. Basic literacy was required, because individuals who could not read the study material and consent form were excluded. However, unlike some other challenge studies (see African HCS above) where medical students were considered ideal candidates, the research group tended to avoid preferential recruitment from the healthcare sector after an unfortunate episode in an earlier study where a participant, who was elsewhere employed as a paramedic, was suspected to have self-treated with anti-malarial medication after challenge (Herrera et al. 2009).

Participants in the Colombian HCS were reimbursed for their costs related to participation but, as per Colombian norms, did not receive any further payment. Though they did not financially incentivise participation, the research group reports no difficulty recruiting volunteers. One member of the research team attributed recruitment success to local experiences of clinical malaria and altruism among the local population:

[T]he difference between here, and [the USA] is that [participants in the USA are] doing that for money and here they are doing it because they are convinced, they are altruists. They have seen people suffering from malaria and they want to contribute to solve the problem. It's a significant difference between a volunteer in the States and a volunteer in Colombia. They know we cannot provide any payment, but do it because they are convinced, not because they need money. [Sócrates Herrera, scientist, Colombia]

### ***5.3.3 Burdens (Including Risks to Participants and Third Parties)***

Since the Colombian HCS used wild-type vivax parasites from infected human donors, the authors document an extensive review of possible risks to participants (and/or uncertainties) related to the challenge infection. In consultation with independent experts, they reached a consensus that there are no known cases of non-malaria pathogens being transmitted by *Anopheles* mosquitoes, but the consent process included a discussion of uncertainty related to “exposure to potential unknown pathogens” (Herrera et al. 2009). Blood/parasite donors were tested for known pathogens (as per usual blood bank screening) and excluded if any were detected. Mosquitoes that had fed on blood with co-infections (e.g., falciparum malaria with vivax, or viral hepatitis) were discarded. It is likely that multiple vivax strains were transmitted by challenge; although, to our knowledge, this was not tested. One advantage of not testing/screening for this is better generalisability to wild-type infection. The presence/transmission of multiple strains, furthermore,

does not necessarily increase the risk of symptoms in participants challenged—and local rates of antimalarial resistance are low (in particular, there is no known resistance to cure of the dormant form of vivax). Physical severe adverse effects were rare, but one patient was admitted to hospital overnight (which meets criteria for a severe adverse effect) with an anxiety crisis (see Sect. 3.3.6.1).

With respect to third-party risk, the local city (Cali) is at relatively high altitude and has no local vector mosquitoes, which minimises the risk of transmission. The mosquitoes used for challenge were laboratory-reared, and any escaping the insectary would face a climate inimical to their survival. The study was conducted on an outpatient basis, and the authors requested that participants avoid travel to areas with vectors while infected, in order to minimise transmission to others. Parasitaemia cleared rapidly with treatment, suggesting that post-treatment transmission risks would have been minimal (if participants later had contact with vectors). Follow-up after the studies was of long duration (up to 18 months reported). Three months after the 2014 study, one participant developed vivax malaria and was treated appropriately. Rather than reactivation of the challenge infection, this was presumed to be a new case of malaria resulting from recent travel to an endemic area—but further testing (e.g., genotyping) to confirm this was not undertaken (Arévalo-Herrera et al. 2014). Local researchers interviewed for this project indicated that there has never been a case of vivax relapse judged to be caused by challenge infection in Colombia.

#### **5.3.4 Summary and Outcomes**

The Colombian vivax studies represent a particularly longstanding locally-initiated LMIC HCS program (with support from international collaborators) that, in response to local disease burden, has successfully moved from model development to vaccine testing. The radiation-attenuated vaccine tested by HCS in 2016 showed protective efficacy of 42%, although it required a long and relatively burdensome schedule of immunisation by mosquito bite. At the end of 2018, no field trial had yet cited the 2016 HCS by this group, so it is not yet possible to compare field trial efficacy with that observed in HCS.

Particularly from 2014 onwards, the group has performed a number of secondary analyses on samples collected during HCS, thus maximising the scientific yield per challenge. For example, the researchers used samples from their 2014 study in a later analysis that aimed to quantify any differences of the risk of transmission (by measuring gametocytes, the form of malaria transmitted from humans to mosquitoes) from individuals infected by challenge as opposed to those diagnosed with naturally-acquired infection in the community (Vallejo et al. 2016), which has implications for potential third-party risks of their study design. In contrast to some older data derived from malariotherapy, the study failed to transmit malaria to mosquitoes by feeding them on subjects recently infected by challenge; however, participants from the naturally infected groups were able to transmit malaria to mosquitoes. Since the

authors failed to show infectivity of mosquitoes fed on HCS participants, there would have been a very low risk (if any) of onward transmission of the challenge infections during the study period, even if the participants were to leave the study location and travel to an endemic area while infected. Such data may facilitate third-party risk estimates of future vivax malaria HCS involving the infection model developed by this research team.

## 5.4 Summary of Case Studies

### 5.4.1 *Rationale and Review Process*

We identified 13 published HCS conducted in LMICs from 1992 to 2108. The number and frequency of LMIC HCS is increasing: 11 of the 13 studies were conducted in the last ten years, and more LMIC HCS are currently being considered and/or conducted. Yet these are still vastly outnumbered by HIC HCS, suggesting that LMIC HCS has been a neglected area of research, especially relative to local disease burden. Each of the 13 studies involved a pathogen endemic to the LMIC in which it was conducted, although in 5 publications the HCS was conducted in a non-endemic area within the country. Common reasons for conducting these LMIC HCS were (i) to improve understanding of host-pathogen interactions in an endemic population, (ii) to develop models of infection (for later HCS vaccine trials), (iii) to test vaccines (in 3 studies), and/or (iv) to improve local capacity for infectious disease research.

All of the studies took place within well-established research institutions that had existing collaborative arrangements with HIC institutions with HCS research experience. With the exception of the Colombia vivax program, most LMIC HCS programs to date (9 of 13 studies) have begun by replicating prior HIC HCS in the local LMIC population. Although the LMIC institutions had experience conducting other types of research, significant capacity building was required in order to conduct HCS, including the capacity of local ethics committees to review such research.

Like most HICs, the LMICs in which HCS have been conducted do not have specific regulations governing challenge strains. Regulatory bodies in Sub-Saharan Africa did review the malaria challenge strain used, aided by previous FDA review and approval. In Thailand and Colombia, the local institutions (and, for the Thai studies, the collaborating US institution(s)) were responsible for the quality and safety of the challenge strains used.

### ***5.4.2 Recruitment, Participant Selection, Consent, and Payment***

All LMIC HCS recruited healthy adult volunteers from the local population (and, for one study in Gabon, a sub-population of European expatriates for comparison (Lell et al. 2017)). Depending on the research question, some studies preferentially aimed to include those with acquired immunity from past infection and/or innate resistance to the disease under study—and recruiting from such groups was a notable advantage of conducting the studies in endemic LMICs. Exclusion criteria were designed to reduce risks to participants, including reducing the probability of lasting harm.

In all studies, consent processes involved multiple sessions and/or a formal test of understanding, suggesting a high standard of informed consent. Many studies aimed to recruit students and/or relatively well-educated individuals in order to improve the quality of understanding; however, recent social science work in Kenya has challenged this assumption, suggesting that less educated individuals may be able to provide adequate informed consent (Njue et al. 2018). This is particularly important if/when there are scientific reasons to recruit from highly endemic rural areas in which the average education level may be lower than in (less endemic, or non-endemic) large cities. There are two further issues with recruiting tertiary-educated individuals: firstly, this may lead to the relative exclusion of women, in countries in which women are less likely to receive tertiary education—and this could lead to the results of HCS being less generalisable to women; secondly, students might in some cases feel pressured to agree to participate (e.g., where the HCS is being conducted by researchers from the university/faculty in which the students are studying), which warrants consideration in future HCS designs (whether in HIC or LMIC settings) (Bonham and Moreno 2008).

These LMIC studies, like HIC HCS, involved significant burdens for participants (see below). Payment was usually indexed to burden and to local wages for unskilled labour—with the exception of Colombia, where no payment was offered apart from reimbursement for financial costs incurred by participants.

### ***5.4.3 Burdens (Including Risks to Participants and Third Parties)***

LMIC HCS participation involved a range of types and levels of burdens—including being exposed to risk and experiencing symptoms of infection; monitoring, bodily examinations, and blood draws by study staff; time away from normal activities including, in some cases, long periods of inpatient isolation; and so on.

Though generally uncommon, severe physical symptoms did occur—and they were more likely in participants from less endemic populations (e.g., Nairobi) and those without innate resistance or acquired immunity to the pathogen used. One participant required treatment for psychiatric symptoms. Based on published data

and interviews with relevant stakeholders, no cases of lasting harm related to LMIC HCS were identified. In some cases the burdens of symptomatic infection could arguably have been further reduced by earlier diagnosis and treatment (e.g., through the use of PCR as opposed to microscopy diagnosis of malaria), particularly where this would not undermine the scientific value of the study.

In terms of risks to third parties, since 5 of the 13 studies were conducted with vector-borne pathogens (*falciparum* and *vivax* malaria) in non-endemic areas of LMICs where there are no local vectors, and a further 4 studies were conducted under conditions of strict inpatient isolation (i.e., a total of 9 studies entailed zero or near-zero risks of transmission), only 4 studies posed potential risks of transmission to third parties. These 4 HCS involving malaria in endemic areas of Sub-Saharan Africa, however, would have had low potential for third-party risk due to the short duration of infection and the high local prevalence of, and immunity to, malaria. Some stakeholders felt that such small risks were acceptable, whereas others suggested that they should be reduced still further (see Sect. 3.4).

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