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RESEARCH ARTICLE

Responsible innovation and political accountability: genetically modified mosquitoes in Brazil

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ABSTRACT

In this paper, we analyse the introduction of genetically modified (GM) mosquitoes in Brazil and use this case to probe the notion of Responsible Innovation and its applicability to the development of new public health biotechnologies in the global South. OX513A, a strain of GM *Aedes aegypti* mosquitoes developed by the British firm Oxitec, has been used experimentally in Brazil since 2009, when it was imported into the country as a promising new tool in the fight against dengue. We discuss the regulatory history of OX513A in Brazil, as well as the forms of "community engagement" that have accompanied the release of transgenic mosquitoes. We argue that the conduct of a scientific research project is only part of a broader effort to localize insect biotechnology in Brazil, an effort that has enjoyed very visible support from political authorities across the country. We conclude by arguing that if the framework of Responsible Innovation is to have purchase on this sort of transnational and multifaceted innovation trajectory, it has to include at its centre a strong notion of political accountability.

Keywords: *Responsible innovation; Brazil; genetically modified mosquitoes; dengue; political accountability*

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1. Introduction: Extending "Responsible Innovation"

The framework of Responsible Innovation seeks to chart a path of enhanced public accountability in the face of the uncertainties, ambiguities and dilemmas brought about by scientific and technological change. A key motivation for this endeavour is the desire to bind innovation processes more firmly to societal needs through an open practice of reflexive stock-taking on the incipient, unspoken or otherwise hidden values that animate technoscientific work (Owen et al. 2012; von Schomberg 2013; Macnaghten et al. 2014). In the governance regimes and academic literatures that have begun to incorporate this concept, Responsible Innovation is often characterised by four dimensions: anticipation, reflexivity, inclusive deliberation and responsiveness (European Commission 2012; Owen 2014; Stilgoe et al. 2013). A central premise of this agenda is the desirability of a more substantial and meaningful inclusion of societal actors in the appraisal of new scientific and technological options, from their inception all the way through their deployment (Davies et al. 2009).

So far, the concept of Responsible Innovation has been theorized primarily in relation to scientific research or technological development projects sponsored by institutions in the global North. Sympathetic critics have noted the need to engage with a broader conceptualisation of innovation (de Saille and Medvecky 2016; Parkhill et al. 2013), and specifically with the global or transnational nature of much of contemporary technoscience (Anzaldo Montoya and Chauvet 2016; Wickson and Forsberg 2014; Blok and Lemmens 2014; Wong 2016). Yet relatively few studies have examined cases outside Europe and North America, and the literature offers little practical advice on the potential challenges of doing so (Chaturvedi et al. 2016; de Hoop et al. 2016; Voeten et al. 2014).

In this paper, we explore some of the conditions that shape the applicability of this framework in a global South context, specifically in relation to the transnational development of technologies that are expected to address public health emergencies. Our case concerns the introduction of genetically modified (GM) mosquitoes in Brazil and their role in the fight against dengue and other mosquito-borne diseases. Since 2009, a strain of GM *Aedes aegypti* mosquitoes developed by the British biotechnology firm Oxitec Ltd. (Oxford Insect Technologies) has been used experimentally in the states of Bahia and São Paulo. *Aedes aegypti*

mosquitoes are responsible for the transmission of several arboviruses, including dengue, chikungunya and, more recently, Zika. The strain developed by Oxitec, OX513A, incorporates in its genome a lethal transgenic construct that renders its progeny nonviable. Provided they are able to mate successfully with wild-type females, the release of large quantities of transgenic males should help supress the local mosquito population and reduce the rate of disease transmission. Brazil has been a key testing ground for this biotechnological method of vector control, which now appears poised for widespread use across the Americas and elsewhere (e.g., Alvarez 2016).

The example of GM mosquitoes in Brazil offers an opportunity to explore how the framework of Responsible Innovation can be applied to technologies that straddle and connect multiple political jurisdictions and innovation domains. A technology first developed in an academic context in the United Kingdom – Oxitec was established in 2002 as a spin-out of the University of Oxford in order to commercialise research from the University's Department of Zoology – travels to Brazil with the expectation that it will quickly become an effective tool of mosquito control at a time when the country is in the grip of a severe dengue epidemic. Not only must the technology in question traverse different political contexts, but the very nature of the innovation is in flux, as the OX513A strain is adapted to new environmental and biomanufacturing conditions (cf. Beisel and Boëte 2013; Nading 2015). This fluidity extends to the technology's regulatory status: at the time of its arrival in Brazil there was no precedent for the controlled introduction of a transgenic insect in the country, let alone one that serves as the vector of multiple infectious diseases. This lack of precedent extended to the design of appropriate mechanisms for public consultation, specifically in and around the sites where GM mosquitoes were to be released.

As we will argue, the complex and conflict-ridden trajectory of OX513A mosquitoes in Brazil serves to highlight the role that *political accountability* in any effective implementation of the principles of Responsible Innovation. By political accountability we mean the existence of a set of mechanisms, institutional or otherwise, that render open to public scrutiny and debate the rationales that actors in positions of political authority draw on to support certain innovation trajectories. These mechanisms may encompass, but are not reducible to, activities that seek community consent or regulatory authorization for specific scientific and technological projects. In fact, one of the most striking lessons from the history of OX513A in Brazil so far is that the motivations and calculations that drove political authorities to invest in

the development of biotechnological methods of vector control were never subject to the sort of reflexive appraisal that the Responsible Innovation framework recommends for the governance of technoscientific change. In particular, the processes of "community engagement" promoted by the sponsors of the technology neither encouraged inclusive deliberation nor gave rise to opportunities for responsiveness to public concerns on the part of innovation actors. At the same time, the regulatory system never explicitly reviewed public expectations or concerns in its assessment of OX513A mosquitoes. The example of GM mosquitoes in Brazil thus exemplifies the need to extend the notion of Responsible Innovation beyond the appraisal of individual research and development projects to encompass the forms of political reasoning that often provide these projects with their ultimate raison d'être.

The account that follows is based on interviews with scientists and regulators involved in the development of GM insects and their introduction in Brazil, as well as on documentary research into the regulatory career of OX513A mosquitoes in the country. We also collected and analysed press and regulatory materials (in English and Portuguese) describing the progress of GM mosquitoes in Brazil between July 2010 and April 2016.

2. The return of dengue and the birth of *Projeto Aedes Transgênico*

Dengue reappeared in Brazil in 1986. For more than two decades, the country had been virtually free of the disease, the result of a vigorous campaign of vector control that started in the 1950s and relied heavily on the use of Dichlorodiphenyltrichloroethane (DDT) and other residual insecticides (Magalhães 2013). The dismantling of mosquito abatement programmes in the 1970s, combined with a rapid process of urbanization and growing mosquito resistance to organochloride pesticides, created new opportunities for *Aedes* mosquitoes to spread throughout the country and entrench themselves in population centres (Rodriguez-Barraquer et al. 2011).

Since the late 1990s the public health burden of dengue has grown exponentially. Four virus serotypes have been detected in the country, and the incidence of haemorrhagic fevers, the most severe form of the disease, has grown significantly, particularly among children (Cantão 2012). In 2014, national authorities reported 590,000 cases of dengue and attributed nearly 400 deaths to infection by the virus (Ministério da Saúde

2015). The country now presents the highest incidence rate of the disease in all of the Americas (WHO n.d.).
In the absence of effective medications – there are no drugs effective against dengue, and the first vaccine, Sanofi's CYD-TDV, was only registered in Brazil in December 2015 – the fight against the disease continues to hinge on the ability to suppress the mosquito vector (Pontes and Ruffino-Netto 1994). The 2002 National Dengue Control Program (PNCD) instituted locally coordinated spraying campaigns, but failed to dent the spread of the disease. A serious epidemic outbreak in Rio de Janeiro in 2008 prompted a new series of national directives that had a similarly limited impact on the rate of transmission.

This was the context in which in 2009 Moscamed, a not-for-profit organisation dependent on the Brazilian Ministry of Agriculture (Ministério da Agricultura, Pecuária e Abastecimento), launched the *Projeto Aedes Transgênico* (PAT), a collaboration with Oxitec and researchers from the Universidade de São Paulo designed to assess the potential use of GM *A. aegypti* mosquitoes in Brazil. The partnership followed several meetings between Oxitec and Brazilian authorities, some of them sponsored by UK Trade and Industry (UKTI), a British government agency dedicated to supporting export ventures by British companies (GeneWatch 2012).[1]

PAT would bring to Brazil Oxitec's patented RIDL method for the genetic modification of insects. RIDL stands for 'release of insects carrying dominant lethals,' and encompasses a series of techniques for inserting into insect genomes mutations that cause the death of the organism's offspring. The lethal mutation incorporated into the OX513A strain is conditional, or repressible, because the expression of the transgenic construct can be neutralised by feeding the mosquito the antibiotic tetracycline. The ability to repress the activation of the transgenic element allows the large-scale manufacture of modified insects in the laboratory, and ensures that GM specimens will not survive long after their release, provided they cannot find tetracycline in the environment.[2]

Oxitec has promoted RIDL as an evolution of traditional insect sterilisation techniques, or SIT (Alphey 2002; see also Alphey et al. 2010). SIT programmes, in operation since the 1950s, use radiation or chemicals to sterilise large numbers of insects, which are then released to reduce the wild population of the target species. With the advent of RIDL and other techniques of genetic modification, mosquitoes can be made 'sterile' by direct manipulation of their genomes, thus allowing greater

specificity in the alterations introduced in the organisms. Direct genetic manipulation also creates new forms of traceability for the modified insects. The OX513A strain, for instance, contains a fluorescent marker gene – the DsRed2 gene from the marine coral species Discosoma – that facilitates the identification of transgenic specimens (cf. Lezaun 2006).

Despite a tradition of SIT programmes in Brazil – Moscamed has been involved in insect sterilisation campaigns for the control of agricultural pests, most notably the Mediterranean fruit fly – the prospect of introducing GM mosquitoes in the country threw up some unprecedented challenges. When the PAT partners announced their intention to bring OX513A mosquitoes to Brazil, there was no obvious regulatory pathway for the evaluation of a transgenic organism capable of carrying and transmitting multiple pathogens. In September 2009, the National Biosecurity Technical Commission (Comissão Técnica Nacional de Biossegurança, or CTNBio), a governmental advisory body on biosecurity matters and the authority in charge of reviewing applications for the introduction of GM organisms in the country, began to create such a pathway by authorising the importation of three batches of OX513A eggs from Oxitec's production facility in Abingdon, UK.[3] These batches – each of them containing five thousand eggs – were earmarked for contained use within Moscamed's 'biofactory' in the city of Juazeiro, in the state of Bahia (CTNBio 2009; see also Reis-Castro and Hendrikx 2013). In parallel to CTNBio's authorisation, Oxitec obtained permission from the UK Department for Environment, Food and Rural Affairs (DEFRA) to export GM mosquito eggs to Brazil for use in contained facilities. Because the mosquitoes were not intended for open release, the authorization for their international travel did not require a risk assessment specifically tailored to the environmental conditions of the importing country (Marshall 2011).

This was a significant juncture in the history of insect biotechnology. Around the time of its agreement with Moscamed, Oxitec was conducting the first-ever experimental releases of GM mosquitoes, on the Caribbean island of Grand Cayman. This study, designed to measure the efficacy of the OX513A strain in reducing the density of the local *A. aegypti* population, proceeded with very little, if any, media coverage outside the island. Furthermore, since the Cayman Islands is a British overseas territory not bound by the UK's ratification of the Convention of Biological Diversity, Oxitec and its Caribbean partners were exempt from the notification procedures concerning the transboundary movement of living modified organisms that are enshrined in the Convention's Cartagena Protocol on Biosafety (United Kingdom Parliament 2010). The

releases in Grand Cayman were made public by Oxitec at the annual meeting of the American Society of Tropical Medicine and Hygiene held in Atlanta in November 2010, once the trial had been completed. Before the end of the year, Oxitec initiated a second set of open field releases in Malaysia (Subramaniam et al. 2014).

The international scientific press covered the news from Grand Cayman at length, and the tone of the coverage was often critical of Oxitec and of the secrecy with which the releases had taken place. A news article in the journal *Science* noted that news of the releases had 'taken aback opponents of GM mosquitoes and surprised many researchers in the field of genetic control of insect vectors' (Enserink 2010). The journal reported unease among some of Oxitec's collaborators, and suggested that the manner in which the trial had been conducted had 'strained ties' with the Bill and Melinda Gates Foundation, a key funder of research on GM mosquitoes. In an editorial entitled 'Letting the bugs out of the bag,' the journal *Nature* criticised Oxitec for conducting the first open field trial of the technology in a country known for its minimalist approach to environmental regulation, and chastised local authorities for conducting the experiments without proper public consultation:

> Efforts by the Cayman Island authorities [to inform the public about the nature of the releases] seem to have amounted to not much more than producing little-reported leaflets and a video, posted on YouTube and broadcast on television, which failed to say that the mosquitoes were genetically modified – the main concern of critics (Nature Editorial 2011, 39).

Warning that 'early buy-in and support from local communities' was essential for the future acceptability of the technology, the editorial called on the scientists working on the development of GM mosquitoes 'to ensure that the relevant authorities make the relevant facts available, or do so themselves.' 'So far,' the *Nature* editorial concluded:

> GM mosquitoes and other insects have largely flown beneath the radar. That will change sooner or later. It is surely better that the scientists involved bring them to the public's attention, rather than have that attention thrust upon them by others (ibid, 39).

Heeding multiple calls to clarify the international regulatory context, the World Health Organization (WHO) announced in 2010 the forthcoming publication of a set of guidelines that would spell out criteria for the safe testing of transgenic mosquitoes, including the conditions under which open field releases could proceed and the ethical and public consultation

protocols that should accompany any such trial. It would take WHO another three years, however, to produce a final guidance document (WHO 2014). In the meantime, *Projeto Aedes Transgênico* would evolve in the absence of an agreed international framework for the assessment of GM insects.

3. Demonstration trials in Bahia

As the controversy over the first outdoor release of GM mosquitoes unfolded in the international scientific press, the partners in *Projeto Aedes Transgênico* were planning an initial open field trial in the state of Bahia. The trial would serve to assess the capacity of transgenic specimens to survive in the local environment and mate successfully with wild-type counterparts. It would also allow the sponsors of the project to calibrate the protocols for the in-time manufacturing and post-release monitoring of GM mosquitoes.

The intention to release OX513A mosquitoes required a series of regulatory decisions on both sides of the Atlantic. Under the Cartagena Protocol on Biosafety, the transboundary movement of living modified organisms destined for direct introduction into the environment must follow an 'advance notification' procedure. CTNBio reviewed a request for release submitted by Universidade de São Paulo (USP) researchers and granted its authorisation in December 2010. In the UK, Oxitec applied to DEFRA for permission to export GM mosquito eggs intended for release. As part of this application, Oxitec included a document detailing the steps that would be taken to minimise the potential environmental risks posed by the liberation of GM mosquitoes (House of Lords 2011).[4]

The suburbs of Itaberaba and Mandacaru in the city of Juazeiro were selected as the location of the releases. The choice was made in consultation with municipal and state-level health authorities, who thought residents in those areas would be "very open to new initiatives regarding public health and development programs" (Capurro et al. 2016: 10365). Contrary to existing advice on this matter (Lavery et al. 2008; see also Ramsey et al. 2014), site selection was not preceded by any public consultation, nor did it seek any form of community authorisation beyond those provided by existing administrative bodies.

Once the site of the releases had been decided, the sponsors of PAT launched what they described as "a vigorous and proactive community

engagement campaign" (Carvalho et al. 2015, p. 4). The campaign encompassed a diverse array of activities, including extensive media coverage for the project. This is how Oxitec describes these public outreach efforts:

> Community engagement remains a key component of the programme. This cuts across all levels of the community from national, regional and local stakeholders, public health and vector control agencies, and the resident community. Engagement with media via radio, TV and press at local and national level has been vital for communication to as many people as possible. In a country that suffers hugely from dengue, media interest remains high with continued, overwhelmingly positive support for the project from all sectors. In addition to working with the national regulatory system, numerous meetings and seminars have been organised with public health and political leaders at all levels to provide information and opportunity for feedback (Oxitec 2011).

As the quote suggests, "community engagement" was a broad category that included extensive media exposure and regular contact with government officials and regulators. Media interest in the releases was indeed considerable and went well beyond local and national outlets. In May 2011, for instance, the trials in Juazeiro were the subject of a special edition of the BBC World Service's flagship science programme *Discovery*. In September of that year, *Projeto Aedes Transgênico* occupied the front page of *New Scientist*. While local and international reports did address some of the potential risks posed by the releases and gave voice to Brazilian critics of the technology (such as AS-PTA, the *Assessoria e Serviços a Projetos em Agricultura Alternativa*), the coverage was for the most part cautiously positive. The GM mosquitoes were "mutant armies waging war in the wild" (Nicholls 2011). They represented "a revolutionary new approach" poised to deliver "a killer blow to the dengue-carrying mosquito" (BBC World Service 2011; see Bustamante 2011 for an example of critical coverage in the Brazilian press).

The other key component of the community engagement campaign was direct communication with residents of the areas where the GM mosquitoes were being released. Members of the PAT team conducted extensive house and school visits to inform local residents of the purpose of the releases. Significantly, this component of the public outreach programme was carried out in parallel to the scientific work of the project. The extensive monitoring required by the trial – in particular the installation and weekly replacement of ovitraps in hundreds of houses in

each of the two suburbs – offered the primary occasion for discussions with local residents.

> [T]here is no substitute for face-to-face interaction on an individual basis, allowing specific questions to be addressed and for direct feedback and concerns to be aired. Intensive monitoring provides ample opportunity for field staff to discuss the project with residents in their homes as they survey the local mosquito population. In addition, dedicated teams have conducted door-to-door visits of every residence to discuss the project, allowing a high level of community engagement. These combined efforts have resulted in visits to every residence in the field site, often on multiple occasions, ensuring the highest level of community engagement possible (Oxitec 2011).

It was clear that the sponsors of *Projeto Aedes Transgênico* were keen to avoid the sort of criticism that had been levelled against the release of Oxitec's mosquitoes in Grand Cayman. It is also clear, however, that the model of consultation implemented during the releases in Juazeiro was narrow in its scope and objectives, and offered little opportunity for inclusive deliberation and responsiveness. Local residents were informed of the purpose of the releases, whether through media outlets or in face-to-face meetings, and they had opportunities to ask questions or offer feedback. Yet in most cases, this information was being provided while the trial was already underway, and it was apparent that the essential parameters of the intervention – site selection, extent and purpose of the releases, monitoring plan – had been decided in advance of any meaningful public consultation and were not subject to significant revision or redefinition in light of local reactions. It is telling in this regard that, as the above quote indicates, the sponsors of *Projeto Aedes Transgênico* thought they were in a position to determine what was "the highest level of community engagement possible."

The limitations of the community engagement model adopted for the first open field trial of OX513A are particularly significant if we consider that the releases were receiving at the same time very visible political support from local, regional and federal authorities. Under growing public pressure to deliver effective measures against dengue, a significant amount of political capital was to be gained from showcasing a new technology in action, even if it was in the guise of a scientific trial. In April 2011, for instance, the governor of the state of Bahia, Jacques Wagner, visited the trial site and pledged his backing for the initiative.

> "The state government supports this initiative and believes that this is another way to fight dengue. For this reason the Secretary of Health, the Secretary of

> Agriculture and the Secretary of Science and Technology are enabling ways to further help this work" (Moscamed 2012; translation by the authors).

During the governor's visit, the State Secretary of Health personally released "about a thousand mosquitoes" in Itaberaba. The support of local state institutions – what PAT researchers describe as the significant amount of "political good will" enjoyed by the project (Capurro et al. 2016: 10365) – was not merely symbolic: the state of Bahia had agreed to fund all the costs of the project, including the purchase of OX513A mosquitoes from the UK.

The releases in Itaberaba and Mandacaru concluded in the summer of 2012. According to its sponsors, the trial had achieved a very substantial reduction in the number of mosquitoes in the area where OX513A males had been released.[5] That same summer, Moscamed inaugurated a new facility in the city of Jacobina, south of Juazeiro, with the purpose of increasing the scale of GM mosquito rearing. The opening ceremony for this new 'biofactory' provided another opportunity for local and national politicians to show their support for the project. Among those attending the inauguration were the Minister of Health of Brazil, Alexandre Padilha, the State Secretaries of Health and Science, Technology and Innovation, and a representative of the federal Ministry of Science and Technology. At the ceremony, Mr. Padilha declared:

> We stimulate the development of this project and will follow it closely, because it promises to be an effective alternative to control the main urban epidemics in the country. Our expectation is to have this kind of technology be complementary to others [methods] to control dengue, and then we will be able to improve diagnostics and treatment. This is why we need to bet on new technologies. [6]

PAT was also winning plaudits from British officials. In September 2012, during a trade mission to Brazil led by British Prime Minister David Cameron, UK Trade and Investment Minister Lord Green heralded Oxitec's growing operations in the country as an example of successful British technology abroad. "I congratulate Oxitec," Lord Green remarked, "for securing new partnerships in Brazil. Getting more companies exporting is a crucial part of the Government's plan for growth" (Oxitec 2012c).

Moscamed's new production facility would be instrumental in the next and final phase of *Projeto Aedes Transgênico*, the large-scale release of OX513A mosquitoes in the city of Jacobina. This would be the first open field trial conducted in a dense urban setting in the midst of a dengue

outbreak, and it was to involve significantly larger quantities of mosquitoes – the original plan called for the release of 4 million male specimens per week for a period of two years.[7] The releases commenced in June 2013, and were accompanied by a series of community engagement activities similar to those carried out in Juazeiro, focalised once again on gaining consent from residents for the installation of mosquito traps. In the words of a Moscamed technical consultant:

> We developed a plan for publicising the project with home visits, lectures in city schools and communication through local media outlets, so that the population is aware of the stages of the project and will be happy to open their homes to the installation of monitoring traps (quoted in Oxitec 2012b).

In addition to door-to-door visits, the sponsors of PAT deployed a series of visual props, including large mascots representing *A. aegypti* mosquitoes, to convey information about the experiment – to 'publicise' it, in the words of the consultant quoted above. The truck used for the releases, for instance, was equipped with loudspeakers that played a jingle explaining the experiment to the public, announcing the trial literally as it was taking place. These outreach activities were carried out primarily by local staff – foreigners rarely talked about the project to local residents or the press, and there was a clear attempt to brand the study as a national, Moscamed-led effort.

The trial in Jacobina unfolded against worsening public health conditions. In February 2014, the city's mayor declared a state of emergency due to the growing number of dengue cases in the area. Across the country, the incidence of dengue would more than double in 2015 (Ministério da Saúde 2016). The threat posed by *Aedes aegypti* mosquitoes was soon compounded by the realisation that the species was also responsible for the transmission of the chikungunya and Zika viruses.

4. Localizing GM mosquitoes in Brazil

Projeto Aedes Transgênico offered Oxitec an opportunity to bring its technology to Brazil and adapt it to local conditions. Oxitec has discussed this process as being much more than an effort to export OX513A mosquitoes, or to transfer a ready-made technological solution to Brazil. PAT was, in their words, an attempt to *localise* insect biotechnology in Brazil.

> A key part of Oxitec's ambition is that our technology can be transferred into other countries such that programmes can be carried out locally. This not only contributes to reducing the threat posed by the dengue mosquito, but it also reduces the overall cost and importantly creates new employment. This 'localisation' of our technology has been a key feature of the Brazil collaboration. In recent months several new jobs have been created in Juazeiro where mass rearing, release and monitoring processes have been established and refined. Oxitec has been working very closely with Moscamed and USP to train staff and create a high quality local facility (Oxitec 2012a).

As the quote suggests, localisation implied the adaptation of the RIDL method to local manufacturing conditions, a process that required the training of local staff and the development of adequate mosquito rearing protocols in local 'biofactories' (Carvalho et al. 2014). This process allowed Oxitec to expand the geographical reach of its technology, and in the process created new employment opportunities in the areas where GM mosquitoes are bred and released.

Localisation also included the development of a regulatory pathway for GM insects in Brazil. A landmark moment in this process was achieved in April 2014, when CTNBio authorised the *commercial* release of OX513A mosquitoes on the basis of their 'intrinsic safety and negligible environmental risk':

> We may conclude…, based on the evidence submitted by [the] applicant, related literature and our risk assessment, that the OX513A *Ae. aegypti* mosquito poses no additional risks to the environment, human beings and animals when compared to the same non-GM species. Our opinion is thus favorable to its release (CTNBio 2014, 9. Translation by the authors).[8]

As relevant as the decision to allow the commercial release of OX513A mosquitoes was the manner in which CTNBio framed the matter at hand. The agency was emphatic that its remit was strictly limited to the issue of safety, and that the best way to answer this question was by comparing the risks posed by mosquitoes of the OX513A strain to those posed by wild-type specimens of *A. aegypti*. Questions about the efficacy of GM insects as an effective tool for the control of dengue, CTNBio noted, where outside the scope of its inquiry and belonged instead to political authorities at the state and federal level:

> [T]his opinion does not focus [on] issues of technological efficacy, costs and advantages/disadvantages as against other technologies of *Aedes aegypti* population control. Finally, questions directly linked to dengue control do not concern CTNBio, but the [Federal] Ministry of

> Health and the [State] Secretariats of Health that may decide to adopt the technology to control this endemic disease (CTNBio 2014, 9. Translation by the authors).

The rhetorical demarcation of a narrow domain of safety, and its separation from questions of technological efficacy, economic efficiency, or political legitimacy is a common strategy of regulatory agencies tasked with the governance of GM organisms (Jasanoff 2011; Hartley 2016; Lezaun 2011). The decision to determine the question of safety on the basis of a direct comparison with the risk profile of a conventional or non-GM variety of the organism under review is also a classic example of the application of the principle of substantial equivalence to the assessment of biotechnological life forms (Levidow et al. 2007).

Yet in the context of the introduction of GM mosquitoes in Brazil such a narrowly framed assessment had significant ramifications. For one, it implied that the OX513A strain ought to be evaluated as a discrete and self-standing technology, rather than in terms of the balance of costs and benefits that GM mosquitoes would introduce within the broader effort to control dengue. An assessment of cost-effectiveness would have required a comparison with alternative approaches to mosquito control and dengue prevention, including a consideration of their potential interactions. Since CTNBio refused to examine this question, there was no regulatory venue for a public appraisal of how the introduction of GM mosquitoes might impact traditional measures of personal protection, for instance, or the sort of spraying and habitat-reduction campaigns that had been used so successfully in the 1960s and 1970s (cf. Lezaun and Porter 2015; see also Lezaun and de Koning 2015).

Furthermore, CTNBio's decision elided a factor that, as we have seen, had been essential to the progress of the technology, namely the very significant and very visible amount of political support GM mosquitoes were receiving from public officials. CTNBio's ruling explicitly indicates that responsibility for the decision to promote the technology as an effective means of dengue control lies elsewhere. Yet, by reducing the issue of safety to the risks directly and 'intrinsically' posed by GM mosquitoes, and by abstaining from any evaluation of the reasons used to justify this approach to dengue control in the first place, CTNBio's framing of regulatory action foreclosed an opportunity to review these rationales in a publicly accountable manner.

Once CTNBio issued its decision on OX513A, the only missing piece of the regulatory puzzle was the final commercial registration of GM mosquitoes, which would have to be provided by the Brazilian National

Health Surveillance Agency (Anvisa), the governmental body responsible under the Brazilian Biosafety Law of 2005 for the registration and commercial supervision of GM organisms with direct implications for human health. Anvisa's involvement in the regulation of OX513A mosquitoes implied that they would be considered a medical technology. This had important implications: the remit of Anvisa's evaluation was broader than CTNBio's, and would include not only the 'intrinsic safety' of the transgenic organism in question but also its effectiveness as a public health intervention.

Pending a commercial registration, however, Oxitec was still able to carry out further releases, provided these could be construed as part of a scientific project and were subject to the level of supervision appropriate to research activities with transgenic organisms. In July 2014 Oxitec opened its own production facility in Campinas, in the state of São Paulo, and gained the capacity to produce transgenic mosquitoes without the collaboration of Brazilian partners. That same year, Oxitec announced a new project in the city of Piracicaba, not far from Campinas. Known as the 'Friendly *Aedes aegypti*' initiative (*A. aegypti* do Bem), this was the first partnership between the company and a local authority. It involved the release of large numbers of GM mosquitoes in the neighbourhood of CECAP/Eldorado, one of the areas of Piracicaba with the highest incidence of dengue.

The trial in Piracicaba was initially delayed by initiatives from several civil society organisations. The Conselho Municipal de Defesa do Meio Ambiente (Comdema) requested the suspension of the releases until Oxitec and the municipality were able to provide conclusive evidence that they would entail no risk to human health or the environment.[9] In parallel, the Society for the Protection of the Environment (SODEMAP), a non-governmental organization that includes among its members several researchers from the Universidade de São Paulo and former members of CTNBio, submitted a civil action to the office of the Public Prosecutor in Piracicaba demanding an official and impartial evaluation of the data submitted by Oxitec to the municipal authorities as part of its application to release GM mosquitoes in the city. The two initiatives were evidence that, by 2015, GM mosquitoes had become a matter of visible public concern in Brazil, and that some civil society organisations expected greater independent scrutiny of the conditions under which open field trials were being conducted.[10]

The releases in Piracicaba eventually commenced in April 2015, and were accompanied by an information campaign conducted jointly by

Oxitec and the municipal authorities. In the words of Piracicaba's Secretary of Health:

> During this period, municipal health workers and the Oxitec team visited a good proportion of the homes in CECAP/Eldorado talking about the 'Friendly *Aedes aegypti*' and reinforcing the importance of people continuing to eliminate breeding sites, keep their houses clean and follow the guidance of the municipal officials to avoid the proliferation of the mosquito that transmits dengue and chikungunya (Oxitec 2015).

The project partners also commissioned a survey of local residents. The data showed overwhelming support for the initiative ("92.7% of Piracicaba citizens support the use of innovative tools to combat dengue and 88.5% support the use of the 'Friendly *Aedes aegypti*'").[11] In the summer of 2016, local authorities reported a 91% drop in the number of cases of dengue registered in CECAP/Eldorado since the start of the releases, and announced an extension of the trial to 11 downtown districts, an area comprising over 60,000 residents (Oxitec 2016).

Importantly, the trial in Piracicaba became the highest-profile open field experiment with GM mosquitoes – in Brazil or anywhere in the world – at the very moment when the public health impact of the Zika virus was becoming apparent. Oxitec and the municipal authorities were keen to showcase the 'Friendly *Aedes aegypti*' project as an exemplar of what biotechnological methods of vector control could accomplish in the fight against this new scourge. Piracicaba soon became a destination for journalists from around the world willing to report on 'the front lines' in the 'war against mosquitoes' (Sifferlin 2016; see also Pollack 2016).

The new threat of Zika energized arguments in favour of insect biotechnology in Brazil, and mobilized further institutional support for GM insects. In February 2016, the President of Brazil, Dilma Rousseff, visited the facilities of Moscamed in Juazeiro. During her visit, the president of Moscamed, Dr. Jair Virginio, emphasised the "proven" quality of the technology:

> We have proven results on the technology of transgenic mosquitoes related to the project developed by Moscamed, including monitoring, public awareness (communication of project milestones), release of mosquitoes on the basis of the geography of the study area, climatic factors, and finally the presentation of results achieved to public institutions and to the community in general. (Quoted in Moscamed 2016. Translation by the authors).

In April 2016, Anvisa granted Oxitec a special temporary registration (*Registro Especial Temporário*) authorising further research-related uses

of OX513A across Brazil. Under the conditions set in this license, Oxitec and any public authority sponsoring the use of GM mosquitoes were still under the obligation to monitor all releases and to submit data to ANVISA on a regular basis. A final commercial registration awaited further scientific evidence and the development of an appropriate regulatory framework (Lopes 2016).

Yet, the Zika outbreak also brought unexpected complications to the roll-out of GM mosquitoes in the country. In late 2015, messages and postings began to circulate in social media linking the sudden emergence of the new disease to past releases of GM mosquitoes in Bahia and São Paulo. Scientific experts were quick to dismiss the alleged connection, but the wide circulation of these rumours raises questions about the effectiveness of past (and future) community engagement efforts. As GM mosquitoes acquire a higher public profile in the country, not least as a result of the vigorous promotion of insect biotechnology by political authorities, the design of processes of inclusive deliberation and mutual responsiveness has become an increasingly complex and critical affair.

6. Discussion

Since the launch of *Projeto Aedes Transgênico* in 2009, the introduction of OX513A mosquitoes in Brazil has invoked many different forms and meanings of 'innovation.' In public presentations, and particularly in the international scientific press, PAT was often construed as a *scientific endeavour*, a research project geared towards the production of more evidence on GM mosquitoes and their capacity to suppress local vector populations. A small but telling example of this particular construction is the fact that the leading partner in all the applications submitted to CTNBio was always an academic institution, the Instituto de Ciências Biomédicas da Universidade de São Paulo, and that these submissions defined the proposed use of GM mosquitoes as a scientific undertaking designed to produce new data. The criteria used by Brazilian and UK agencies to authorise the arrival and initial development of OX513A mosquitoes in the country were those pertaining to the safe conduct of a scientific experiment. In the absence of a final commercial registration, OX513A mosquitoes continue to be released in Brazil under the terms of a temporary research licence.

Other actors, however, have consistently presented PAT as a *technology development project*, an effort, supported by state institutions, to adapt a novel genetic vector control method to the specific conditions of Brazil. This adaptation involved the transfer of technical skills and production capacities from the UK, a process that Oxitec viewed as an opportunity to extend its operations and products into a promising new market and that many in Brazil saw as the starting point for a national infrastructure of insect biotechnology. Early questions about Oxitec's willingness to license the technology to its Brazilian partners suggest that this particular innovation trajectory was beset from the start with conflicts about the scope and benefits of the partnership.

Simultaneously, PAT represented to its sponsors a *marketing opportunity*, a way of advertising the potential of the OX513A strain as an effective tool against dengue and other mosquito-borne diseases. This marketing effort overlapped to a significant degree with the "community engagement" campaigns launched alongside the open field trials. These campaigns sought to inform relevant stakeholders and residents of the trial sites of the purpose of the releases and their intended benefits. The interest of Brazilian and foreign news organisations in the experimental releases carried out in Brazil transformed the country into the global testing ground for Oxitec's technology, and for genetic methods of vector control more generally. Much of what the world knows today about the

use of GM mosquitoes as a method of disease control is based on the experience of OX513A in Brazil.

Last but not least, PAT was also a process of *regulatory innovation*, a largely successful attempt to chart a pathway for GM mosquitoes through the Brazilian regulatory system in the absence of international rules or guidelines for their oversight and evaluation. In this regard, OX513A has served as a trailblazer for future insect biotechnology applications, including those in the area of agricultural pest control, where the largest market potential of the technology lies. CTNBio's decision to assess the "intrinsic safety" of OX513A mosquitoes on the basis of a comparison with wild-type *A. aegypti* counterparts, and the procedural exclusion from the agency's remit of questions of cost-effectiveness, represent a far-reaching precedent for the future regulation of GM insects in the country.

All these innovations are bundled together in the recent history of OX513A mosquitoes in Brazil. The element that links them all together, the factor that enabled GM mosquitoes to gain a foothold in Brazil and that explains their progress over the last seven years, is the remarkable degree of support that *Projeto Aedes Transgênico* received from political authorities at the local, state and federal levels. The dengue emergency made GM mosquitoes particularly attractive to political leaders; a great deal of political capital was invested in the successful introduction of OX513A mosquitoes, and a significant amount of political capital was gained from showcasing this technology in action, even in an experimental form, at a time when the country appeared to have no effective tools to halt the spread of the disease. The discovery of the chikungunya virus in 2014, and of Zika in 2015, only enhanced the promissory value of biotechnological methods for the control of *A. aegypti*.

Yet these political calculations have remained under-scrutinised, a behind-the-scenes force that has rarely been subjected to public inquiry. The significant amount of media interest in OX513A mosquitoes and the multiple programmes of "community engagement" undertaken during the open field releases served primarily to "publicise" the releases, rather than to examine the fundamentally political choice to pursue a biotechnological strategy of vector control, or to explore the conditions of public acceptability prior to a decision to deploy the technology. In other words, the processes by which the sponsors of PAT and subsequent projects sought to obtain a degree of community consent to the release of GM mosquitoes were not meant to clarify, articulate or evaluate the reasons political authorities had to put their weight behind the technology

in the first place, nor did they create a venue for collective deliberation on its implications. Growing pressure from civil society organisations eventually found a venue of independent review in the office of the Public Prosecutor, the *Ministério Público*, which has become to play a key role in the evaluation of open field trials and their impact on the public interest.[12]

This is why, in our opinion, the concept of Responsible Innovation needs to be more closely interlinked with a strong notion of political accountability. Political decisions create the conditions of possibility for specific innovation trajectories, within which discrete research and development projects then unfold. The ability to scrutinise these decisions determines whether and how core ideas associated with Responsible Innovation, such as inclusive deliberation or responsiveness, are adopted by innovation actors and, if so, to what effect. The still inconclusive history of OX513A mosquitoes in Brazil suggests that we need to consider more carefully how the calculations that lead political authorities to support specific innovation trajectories can themselves be subject to processes of anticipation, reflexive learning, and inclusive deliberation.

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[1] The partnership was initially going to include the Oswaldo Cruz Foundation (Fiocruz), the preeminent public health research organisation in the country. Ultimately, however, Fiocruz would decide not to participate, citing concerns about Oxitec's reluctance to transfer the technology to its Brazilian partners. Interview with Fiocruz scientist, 23 March 2016.

[2] The possibility that GM mosquitoes will find tetracycline in the environment has been one of the controversial elements of the technology (see for instance Friends of the Earth, 2012).

[3] Part of the Federal Ministério da Ciência e Tecnologia (now the Ministério da Ciência, Tecnologia, Inovações e Comunicações), CTNBio is composed of 27 members, including 12 scientists, 9 officials from government ministries, and 6 representatives of civil society from the following sectors: occupational health, family agriculture, biotechnology industry, consumer representatives, health industry and environment protection NGOs. For an analysis of CTNBio's decision-making process in relation to GM plants, see Braña et al (2012).

[4] The risk assessment document included in the notification is available at https://bch.cbd.int/database/record.shtml?documentid=105833 9last accessed 28 September 2016). It was only submitted to the Cartagena Protocol's Biosafety Clearing House in August 2014 (GeneWatch 2015).

[5] PAT reported a reduction of 95% in the number of adult *A. aegypti* mosquitoes in the area (Carvalho et al 2015).

[6] Bárbara Semerene, "Mosquito transgênico combaterá a dengue." Available at http://femetopsaude.blogspot.com.br/2012/07/inovacao-mosquito-transgenico-combatera.html (Last accessed 28 September 2016).

[7] There was an element of regional politics in the choice of location for the study. One of our interviewees, a former member of CTNBio, suggested that resistance to the releases in the northeastern part of the country, where Jacobina is located, would be lower than in the south.

[8] Two members of the Commission issued a dissenting opinion warning of the public health and environmental risks that could arise if the ecological niche currently occupied by *A. aegypti* were to be occupied by *Aedes albopictus* mosquitoes, an alternative vector of dengue. This dissenting opinion also noted 'the failure to comply with existing legislation; the lack of assessment protocols appropriate to the risk analysis concerning flying insects; the insufficient character of the studies presented, and the absence (in Oxitec's application) of the final results of field studies approved by CTNBio' (CTNBio 2014, p. 10. Translated by the authors).

[9] The president of the Conselho, Sônia Cristina Ramos, stated some of the concerns that prompted the request: 'Would not the mosquitoes in fact breed offspring that can transmit diseases? Would it not be the case that the dengue virus will modify itself and start demanding ways to combat the disease that will be even more complicated? We believe that questions like these should be answered. If there are no risks, Comdema will not be against the liberation of transgenic mosquitoes.' See 'Conselho quer barrar liberação de "Aedes transgênico" em Piracicaba', globo.com (11 March 2015). Translated by the authors.

[10] The review of the Public Prosecutor concluded with the decision to authorise the releases, on the condition that local residents were able to continue to use insecticides and other methods of mosquito control.

[11] The figures are mentioned in an article in globo.com (see Carvalho 2015), which quotes Oxitec (Oxitec 2015).

[12] The story of OX513A mosquitoes in Brazil unfolded at a time of significant institutional turmoil in the country, when questions of political accountability were often at the forefront of public debate. This period culminated (as of September 2016) with the impeachment and removal of President Rousseff on charges of manipulating government accounts.

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