Explaining Variation in Medical Innovation: 
The Case of Vaccines, and the HIV AIDS effort

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Explaining variation in medical innovation:
The case of vaccines, and the HIV AIDS effort

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24th November 2015

Abstract:
This paper highlights two variables, neglected by economists, that I argue are important in explaining patterns of innovation seen in vaccines and perhaps in other parts of medicine too. They are: firstly, the extent to which it is safe to experiment on humans; and secondly, whether good animal models can be identified and used, with the latter especially important if there are strong constraints on experimenting with humans. To consider the argument, the paper discusses the case of vaccines, where the political economy of R&D appears to explain only part of the observed variation. I focus on HIV vaccine development and find that, together, these two variables not only make up a large part of how I would characterize ‘difficulty’ in the HIV R&D process, but they also seem to go a long way towards explaining why 31 other diseases have – or have not - had vaccines developed for them. In characterizing these variables, I discuss what might happen if we choose to persist in difficult R&D domains, finding that development may be forced into trajectories that yield lower-quality products. Counter-intuitively, such lower-quality products are typically costlier because they are harder to pass through clinical trials. Implications for theory and policy are discussed, chief of which are that the technical difficulty of R&D is not fixed and can be shifted by policy, and that difficult R&D trajectories need not be pursued when alternative trajectories exist (or can be developed).

Keywords: innovation, research & development, experiment, governance, vaccines, HIV AIDS, animal models.
JEL codes: O31, O32, O33, O38, D81, D83, I18.
1 The uneven effect of research on practice

Why have we been able to put a man on the moon but not improve the plight of those in the ghetto? That question, posed nearly 40 years ago, remains as troubling today as it was then (Nelson 2011). If anything, it has become even clearer that some fields of human endeavor yield extremely rapid change (e.g. transportation, telecommunications) whilst others remain stubborn challenges (e.g. education, crime) (von Tunzelmann et al 2008; Morlacchi and Martin 2009).

Part of the variation is clearly political and sociological in nature. However, a good deal of the variation we see in improvements in practice is related to the uneven growth of knowledge (Nelson 2003; 2008). The ability to learn from experiment, be it natural or designed, has played an increasingly important role in economic growth and technical change over the last 150 years or so, just after the kink in von Tunzelmann’s Hockey Stick (Mokyr 1990; McCloskey 2013; Nightingale 2014:p13). More recently, since around the time of Nelson’s original formulation of the problem, we have seen deliberate and designed experiment feature much more prominently across vast swathes of industry - such that even the humble razor blade now seems to have its own formalised research and development (R&D) centre.

In this paper I explore how R&D can lead to highly uneven effects on practice. To a certain extent, some appreciation for the variable effect of research on practice is already evident. Biomedical research, for example, commands a high degree of shared appreciation for the role it plays in the development of medicines and their subsequent impact on medical practice and health (Sampat 2012). However, medicine itself also exhibits variation: for example, treatments for cardiovascular disease have improved quicker than for cancer (Lim et al 2012). Looking within cancer treatments also reveal large disparities (e.g. for the breast and lung).¹ One might disregard this heterogeneity in medical innovation simply

¹ Again, some variation is ostensibly political and sociological - lung cancer tends to affect poorer segments of the population than does breast cancer (Anand et al 2004). However, such explanations become harder to sustain when we consider that some lung
by labeling some problems as technically more difficult, but this does not make the question disappear; it merely pushes the analysis further back to what makes research problems more or less tractable. Thus, the central question that began this paper might also be put forth as: what is ‘difficulty’ in R&D?

Even within a single sector, the cognitive and cultural conditions of knowledge growth can give rise to strikingly heterogeneous outcomes (Nelson and Nelson 2002; Yaqub and Nightingale 2012; Nightingale 2014). What sets medicine apart from other sectors of economic activity however, is not only that it is research intensive, or that is it is widely appreciated as being so, but that safety plays a paramount role. Defective technology in this domain can be harmful or lethal. This is of consequential importance because the ability to engage in experimental learning, where safety is not placed in jeopardy, becomes an even more salient variable in explaining variation.

Nowhere is safety more pivotal than in vaccines, a sub-sector of medicine that together with sanitation has largely been responsible for perhaps ‘the greatest benefit to mankind’ (Porter 1997). Vaccination is a technology which is (mostly) given to ‘healthy’ people as a preventive, often people who have extremely low tolerance for anything that might seen as jeopardising their safety (Yaqub et al 2014). As the reader might have anticipated by now, vaccines display heterogeneity too, some are developed quickly and others not at all (see figure 1).

cancer types (non-small cell) and some breast cancer types (T1) are easier to treat than others, or when we consider variation across, say, the 137 types of blood cancer.

2 A vaccine is a substance sufficiently like the disease-causing organism to generate a specific response in the immune system, but sufficiently different that the vaccine itself does not cause the infectious disease. The immune response that is most sought after is one that will protect from future infections, known as acquired immunity.
<table>
<thead>
<tr>
<th>Infectious Agent (disease)</th>
<th>Agent linked to disease</th>
<th>Vaccine licensed in U.S.</th>
<th>Years elapsed</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Influenzae</em> (influenza)</td>
<td>1933</td>
<td>1938 (US Army), 1945 (US general)</td>
<td>5</td>
</tr>
<tr>
<td><em>Measles virus</em> (measles)</td>
<td>1953</td>
<td>1963</td>
<td>10</td>
</tr>
<tr>
<td><em>Salmonella Typhi</em> (typhoid fever)</td>
<td>1884</td>
<td>1896 (British Army), 1914 (US general)</td>
<td>12</td>
</tr>
<tr>
<td><em>Hepatitis B virus</em> (hepatitis)</td>
<td>1965</td>
<td>1981</td>
<td>16</td>
</tr>
<tr>
<td><em>Rotavirus</em> (diarrheal disease)</td>
<td>1973</td>
<td>2006</td>
<td>33</td>
</tr>
<tr>
<td><em>Bordetella pertussis</em> (whooping cough)</td>
<td>1906</td>
<td>1948</td>
<td>42</td>
</tr>
<tr>
<td><em>Varicella zoster virus</em> (chickenpox)</td>
<td>1953</td>
<td>1995</td>
<td>42</td>
</tr>
<tr>
<td><em>Poliovirus</em> (polio)</td>
<td>1908</td>
<td>1955</td>
<td>47</td>
</tr>
<tr>
<td><em>HIV</em> (AIDS)</td>
<td>1983</td>
<td>Not yet</td>
<td>32+</td>
</tr>
<tr>
<td><em>Human cytomegalovirus</em> (birth defects, mononucleosis)</td>
<td>1960</td>
<td>Not yet</td>
<td>55+</td>
</tr>
<tr>
<td><em>Flaviviridae</em> (dengue fever)</td>
<td>1907</td>
<td>Not yet</td>
<td>108+</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em> (tuberculosis)</td>
<td>1882</td>
<td>1927, but ineffective in tropical countries or children</td>
<td>133+</td>
</tr>
<tr>
<td><em>Plasmodium spp.</em> (malaria)</td>
<td>1880</td>
<td>Not yet</td>
<td>135+</td>
</tr>
</tbody>
</table>

The political economy of vaccine R&D investment explains only part of the observed variation. Advocates of increased research funding (Archibugi & Bizzarri 2004) do not explain why poorly funded programmes can succeed while well-funded programmes sometimes fail. Economists often assume demand constrains supply (Esparza et al. 2003; Pauly et al. 1995) and propose advanced market commitments (Kremer et al. 2006), intellectual property incentives (Lanjouw 2003), and Public-Private Partnerships (PPPs) (Buse & Waxman 2001) as solutions. Sociologists, by contrast, focus on anti-vaccination movements (Nichter, 1995; Poltorak et al., 2005; Blume 2006) and social processes for selecting between different technical options for a given vaccine (Blume & Zanders, 2006; Blume & Tump, 2010). Again, these explanations are all relatively silent on why vaccine innovation can be so difficult. Certainly, some diseases
have been subject to market failure, socio-political neglect, and woeful under-investment, but other diseases have not. HIV, for example, has benefited from a lucrative potential market, a high social profile and almost $1 billion a year in R&D; yet an effective HIV vaccine is not anywhere on the horizon of most scientists.

Using theory presented in the next section, I shall argue that the technical difficulty of R&D tasks is sharply influenced by two variables. They are: firstly, the extent to which it is safe to experiment on humans; and secondly, whether good animal models can be identified and used, with the latter especially important if there are strong constraints on experimenting with humans. Together they make up a large part of how I would define 'difficulty' in medical innovation.

The two variables, and their consequences for R&D trajectories, come into view when we adopt a framework that exposes learning in practice and testing in models (presented in section 2). Three empirical sections illustrate how HIV vaccine development in humans is extremely precarious (section 4), placing greater necessity and emphasis on animal models (section 5), and how persistence in this trajectory will have costly implications (section 6). Lastly, I discuss the extent to which variation in vaccines against other diseases can be explained using these two variables (section 7).

2 Testing regimes and their effects on innovation

Medical innovation, perhaps more than any other sector of industrial activity, holds dearly the notion that science is 'translated' into technology. But technology can precede the scientific theories that explain why they work. Steam engines preceded thermodynamics, airplanes flew before aerodynamics, and

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3 A burgeoning literature views clinical knowledge as related but significantly independent from advances in scientific knowledge (Gelijns and Rosenberg 1994; Metcalfe et al 2005; Morlacchi and Nelson 2011; Consoli and Ramlogan 2012). My motive here is to open up an additional line of inquiry into the role of testing in medical practice and its effect on the rate and direction of change (Yaqub 2016; Yaqub and Nightingale 2012).
transistors antedate solid-state physics (see Nelson et al. 2011 for medical examples). This is possible because technologies are not merely applications of science. They are more usefully understood as emerging from a search for ‘operational principles’ (Vincenti 1990:p209), which define how technologies work and imbue them with a purpose, a process that is distinct from the goals of scientific endeavor. It is possible, after all, “to know how to produce an effect without knowing how an effect is produced” (Nightingale 2004:p1271).

Operational principles indicate which set of starting conditions might yield a given desired end-result, and are often found by extrapolating from prior successes (Nightingale 2014:p10). Their application takes the form, ‘phenomena x can be generated using y’, prompting sub-problems (i.e. how to produce y) that iterate to produce a hierarchy of increasingly specific, inter-related problem-solving tasks (Constant, 1980:p24-27; Vincenti, 1990:p9). Failure to resolve sub-problems may trigger a redesign process that involves revisiting problems higher up the hierarchy. These tasks form the basis for an innovation process that will typically involve the costly and time-consuming exploration of various dead-ends to discover which uncertain operational principles work.

An important dimension of innovation therefore lies in deciding how far initial attempts should deviate from established operational principles that are already known to work. In most cases this is a strategic decision that trades off the potential added value of an innovative design against the increased uncertainty and cost implications of redesign (Nightingale 2014:p12). However, unlike other sectors of economic activity, safety plays a paramount role in medical practice, where malfunctioning technology can be harmful or lethal. So deviations from existing traditions of practice are constrained and redesign cycles are permeated with safety considerations throughout.

Even after operational principles have been found, considerable further development is often needed to establish safety under varying conditions. As such, safety and efficacy concerns overlap and interact throughout development. Indeed, many modern innovation processes now involve testing not only to trial
the feasibility of inventions before going into full-scale operation but also to actively develop their products ‘offline’ (Nelson 2008; Sarewitz and Nelson 2008). Though in medical practice, the scope for improvements through actual practice is often severely constrained, and learning through offline testing (in animal models and in humans under highly controlled conditions) becomes an even more important factor shaping the difficulty of innovation. Thus, in medical innovation, offline development serves first and foremost as a way to vicariously explore the safety of putative operational principles.

Offline development of technology has other salient effects too. It allows for rapid and cumulative change through specialization of labour and instruments organized around testing (Constant 1980). Knowledge, specifically oriented to testing, is embodied in people (testing communities and organisations) and artefacts (testing equipment, tools and instruments), which come together in testing sites (wind tunnels, clinical trials etc.).

During offline testing, we effectively move away from passive validation to active experimental intervention (Yaqub and Nightingale 2012:p2144; Nightingale 2014:p13-14). In ‘testing as validation’, testing is quicker but, because it is atheoretical, it offers little guidance about what to do if the technology doesn’t work. Such testing might tell us about the safety and efficacy of a product quickly, but it tells us less about how to redesign and improve the product.5

In contrast, ‘testing as experimental intervention’ is used to build artificial conditions in models, often creating completely new phenomena (e.g. photoelectric, Zeeman, Compton effects were created in physics for theoretical learning) (ibid). The creation of these artificial conditions can range from the highly purified to the more realistic. Learning emerges from the way they are measured and controlled. Simplifying assumptions can be gradually relaxed across a series of model organisms such as yeast and nematode worms through

4 The effect is appreciated by engineers, “About half of the Institution of Electrical and Electronic Engineers annual list of the 200 top innovations is devoted to testing equipment” (Constant 1980:p276).

5 See Brodie-Kolmer failures in Yaqub (2016).
to zebra fish and mice (ibid). This generates a series of experimental stepping-stones, which trade-off ease of learning (simplicity) against clinical relevance (complexity) (ibid).

Models mediate between theory and practice, and have at least two other important characteristics (Morgan 1999). First models are heterogeneous; their variety is useful in that they allow for smaller ‘leaps’ between stepping-stones. However, this very heterogeneity poses a challenge for co-ordination and governance of the research effort (Nightingale and Yaqub 2012; Yaqub 2016). Comparing vaccines using virus types of differing pathogenicity, different delivery routes, in different doses, with different endpoints, might be meaningless. So models need to be standardised to a certain extent, and may serve as gatekeepers before development can progress. 6

Second, models are autonomous bodies of knowledge; that is to say, models are not necessarily given – they are created using instrumentalities (instruments, tools and techniques, see Price 1984). Testing communities build up around practicing old techniques for doing something; produce a new technique by tinkering and fiddling with it; then perfecting, extending and using it on everything in sight (Baird 2004). Occasionally, it is hoped, the testing community will yield a set of conditions that can be used as a new stepping-stone between learning and relevance.7

The virtues of being able to disconnect technical change from its environment need to be set against an important disadvantage. As we shall see in the empirical sections, formalised testing regimes can make the development of products offering only marginal improvements extremely (perhaps

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6 For example, the SHIV-macaque model quickly gained currency and acquired the status of ‘gatekeeper’ for progression to clinical trials (Shedlock et al. 2009).

7 For example, Price noted how the telescope provided the conditions in which Galileo made his contributions, an experience which Price delightfully termed ‘artificial revelation’ (1984:p9). This was not the testing of theories, but rather the trying out of new practices and techniques to create new conditions, hoping for learning opportunities, and then relating them to the world outside of these ‘unnatural conditions’ (1984:p9).
prohibitively) expensive. They can serve to force us into trajectories with less desirable performance characteristics, thereby limiting choices about the direction of technological development (Dosi 1982; David 1985; Stirling 2008; Rip 2012).

3 Methods

I use a deviant (or extreme outlier) counter-theoretical case where key elements in the theory are missing (as deployed in Yaqub and Nightingale 2012). The theory section above suggests that innovation relies heavily on learning through actual practice, and where that option is not viable, innovation relies heavily on being able to move off-line and across a series of stepping-stones before going into practice. I explore a situation where the pathogen is dangerous (limiting learning in practice) and where stepping-stones are missing (limiting ability to move learning offline). I infer about their importance from the extensive governance processes that attempt to ‘substitute for the missing prerequisites’ (Gerschenkron, 1962: p359). I strengthen both internal and external validity by considering how these two key variables affect different trajectories of development (variation within HIV vaccines), and by also considering how HIV vaccine efforts are different to other diseases (variation between vaccines).

The case was selected due to its high profile and R&D funding. The case selection also addresses a paucity of empirical study of failure (Staudenmaier 1985), which exists despite abundant theoretical evidence indicating that the majority of innovation attempts result in failure (Pavitt 1999, or see any handful of the references cited in section 2). While some may consider it premature to describe HIV as a failure-case, it is difficult to regard it as anything more than ‘not yet successful’ when prominent AIDS researchers remark, “the virus is winning” and “HIV is currently beating the crap out of us” (Hilleman 1992: p1052).

My data draws predominantly on scientific reviews and journals, as well as a range of historical sources, practitioners’ accounts, histories, biographies, policy reports, newspaper articles, and publications by NGOs such as advocacy groups,
charities and foundations. The data was collected as part of a larger multi-year study into variation in vaccines and their R&D trajectories (Yaqub 2008).

4 Difficult to explore HIV vaccines in humans safely

“People have been talking vaccine, vaccine, vaccine for public consumption, and I have said it too. But I always scratch my head and say this [AIDS] is not the kind of situation where it is going to be easy to do the testing” (Unnamed US public health official, quoted in Altman 1986).

As with all diseases, when a causative agent is definitively established, hopes for a vaccine flourish. AIDS was no different. When the pathogen causing AIDS was first discovered in 1985, hopes for an HIV vaccine ran so high that the US secretary of health declared that one would be ready in two years (Shilts 1987:p451). Ideas for how a vaccine could work, operational principles, were initially ten-a-penny. But after HIV was examined more closely, it became apparent that it would be extremely difficult to explore the feasibility of these ideas in humans safely. The virus has two important characteristics: its ability to evade ‘natural sterilising immunity’ and its extreme variation.

4.1 Humans lack natural sterilising immunity against HIV

People who recover from a general infection are often able to clear it completely from their bodies, and are immune from subsequent attack by the same pathogen. This is not so for HIV because no-one is known to have completely cleared the infection (McMichael and Hanke 2003; Garber et al. 2004; Girard et al. 2006). ‘Natural infection with HIV does not result in virus clearance by the host immune system and the development of natural immunity to re-infection’ (Girard et al. 2006:p4065). Humans can therefore be said to lack natural sterilising immunity to HIV, with at least two implications.

Firstly, this makes HIV vaccine development unforgiving in the sense that, should a vaccine designer's attempted vaccination mistakenly infect the vaccinated, it
cannot be cleared by the body afterwards. Theoretically, even if the virus was completely cleared, the threat of re-emerging from latency remains.

Secondly, natural sterilising immunity has previously provided clues in the development of vaccines. Its absence means that ‘the potential correlates of protection are not known, leaving us without a definite model of protective HIV immunity to emulate through vaccination’ (Garber et al. 2004:p398). Historically, and with few exceptions, vaccine work begins with an empirical observation about natural protection, followed by attempts to copy or elicit the same type of protection by identifying markers of protection. Sometimes, even when correlates of immunity are unknown, it is possible to forge a vaccine provided there is natural immunity to begin with. For example, it was observed that exposure to cowpox protected people from smallpox, and this observation is what led Jenner to try his experiments. With HIV, neither correlates of immunity nor natural immunity are forthcoming, leaving little for vaccine designers to mimic using vaccine preparations.  

4.2 Extreme variation of HIV creates fast-moving goalposts

HIV is the most variable virus discovered to date (Klein and Ho 2000:304). Influenza is also considered highly variable, but the variation in a single individual six years after HIV infection can be as great as the global variation for an influenza outbreak (Weiss 2003:12). Mutations at every possible (single nucleotide) point in HIV’s genome occur thousands of times per day (Johnson and Desrosiers 2002). Even if suitable targets are found, around which an operational principle for an effective vaccine could be developed, extreme variation has two important implications.

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8There are a few individuals who offer further ways forward. A small cohort of sex workers in Nairobi were found to be exposed but uninfected; however, their immunity was dependent on continued exposure (Nabel 2001:1002; McMichael and Hanke 2003:p875). There are also some infected people who have managed to fend off the onset of AIDS for more than a decade, known as long term non-progressors or elite controllers (Johnston 2000:p268). More recently, in Berlin, an HIV positive patient who took a bone marrow transplant from a patient with rare gene differences for their CCR5 receptor, was able to bring his viral count to non-detectable levels; however, efforts to repeat the effect in six other transplants all failed (Cox 2015).
Firstly, the longer HIV replicates in the host, the more diverse variants evolve, which may then allow the virus to escape immune responses. This serves to reduce the window of opportunity such that, ‘the success of vaccination may hinge on altering events that occur in the early hours following HIV exposure’ (Graham 2002:209). In other words the vaccine needs to clear the infection very quickly – unprecedented in vaccine history.

Secondly, even if an effective vaccine is developed, its efficacy period might be hopelessly fleeting if HIV simply evolves its way out. For reference, a mere 2% discrepancy between a vaccine strain and wild types of influenza virus necessitates the formulation of a new influenza vaccine each year (Garber et al. 2004:p405). Often, by the time an influenza vaccine has been manufactured and distributed, it is already ‘out of date’ and has much weaker efficacy than initially intended.

Suffice to say the two factors alone, lack of sterilizing immunity and extreme variation of HIV, make HIV dangerous enough to rely heavily on animal models for vicarious development. However, the next section shows that animal models are not given - and nor are they inevitable. Their creation and use is contingent on the development of instrumentalities and governance.

5 Difficult to learn about HIV vaccines from animal models

"When it comes to testing HIV vaccines, only humans will do” (British Medical Journal, Tonks 2007).

The drive for animal-led HIV vaccine R&D has been problematic for a number of reasons. Foremost is that HIV is a primate virus capable of infecting only few

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9 There are other technical obstacles that create formidable design specifications for HIV vaccine developers (e.g. HIV targets the immune system itself, infection can be transmitted by virus hidden inside cells as well as by free virus).
animal species. Although HIV infects chimpanzees, it does not culminate in disease (AIDS) (Klein and Ho 2000; Nath et al. 2000).\(^\text{10}\)

Reviews readily acknowledge that ‘we have no truly useful small animal model’ (Gallo 1991:p1894) and ‘the lack of a truly representative animal model’ (Klein and Ho 2000:p304) for HIV vaccine development (see also Nabel 2001; Johnston and Fauci 2007). Yet, the majority of the scientific literature I have reviewed discusses data derived from animals. There is an inconsistency between the complacency about animals and the use of animals. ‘Lacking’ or ‘having a useful model’, are passive descriptions or observations of the state of the natural world as it is, which downplays human agency in their use and interpretation. Girard et al. (2006:p4066) expresses the difficulties more actively, ‘the difficulty [lies] in developing an appropriate animal model.’ This choice of word, *developing*, reflects more of the effort that is expended in creating new effects through experimental intervention.

### 5.1 Learning in animals

Unlike the construction of prototypes and testing chambers in engineering, which are seen as clearly man-made endeavours, the use of animals as is quite rightly not seen in this way because animals are not man-made. But scope for man-made interventions that structure the environment provided by animals does exist, and this role is somewhat understated when barriers to vaccine innovation are being explicitly articulated.

Monkeys were used to guide the way to poliomyelitis vaccines despite the fact that they did not closely mimic what happened in humans (Yaqub and Nightingale 2012). Monkeys do not normally become infected with poliomyelitis, but when injected directly into their brains the virus is infectious and able to paralyse, giving rise to an animal model with clearly visible test results. Isabel Morgan’s experiments therefore facilitated the *development* of monkey models

\(^{10}\) It replicates slower and does not gather in (and destroy) the lymph node architecture as quickly.
such that they could become incorporated into an effective testing regime.

Efforts to understand what conditions animals actually represent consume much of the HIV literature. Unrealistic models remain useful to researchers provided they know what aspects of the vaccine they are testing. For example, chimpanzees do not readily progress to AIDS in a human-like way (Klein and Ho 2000), so the chimpanzee model is not helpful for studying how a vaccine might ameliorate disease progression. Instead, the model is more helpful for testing vaccines that aim to prevent infection outright because chimpanzees can be infected by HIV. Thus the usefulness of a model depends both on our understanding of the conditions that the model presents us with and on our ability to standardise what function is being tested for.

For HIV, many researchers think animal models will never be predictive of overall human effects (e.g. Greek 2012) or, at least, express extreme uncertainty about our understanding of what these testing conditions represent, ‘Even a vaccine that has 100% efficacy in all three challenge models might still be ineffective in humans. Conversely, a proficient vaccine developed in humans might never show benefit in the animal models’ (Nath et al. 2000:430). Similarly Feinberg and Moore (2002:209) caution interpretation of data arising from animals, ‘Animal models cannot determine whether a vaccine will be effective against HIV infection of humans.’ However, they also note that ‘it is essential for models to be improved [my italics].’

5.2 Creating new models

It is evident that researchers do not simply ‘make the best of what they've got’. They intervene by tinkering with them, creating new effects that may be useful

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11 Feinberg and Moore explain, 'For instance, a virus that replicates very poorly in a host [as is the case with HIV-in-chimpanzee models] may be misleadingly easy to protect against by vaccination, and is of little value for studies of viral pathogenesis...Conversely, vaccine studies that employ particularly virulent viruses, as is the case with SHIV-in-macaques [discussed below], or experimental challenges delivered at high doses via intravenous inoculation may underestimate the potential protective efficacy of some vaccine strategies' (Feinberg and Moore 2002:p207).
for technology. For a primate virus that is capable of infecting only few animal species, the craft could include changing the virus, changing the animals, or both. This can be illustrated by the two main animal models used in HIV vaccine development: SIV and SHIV in monkeys.

SIV, the causative agent of simian AIDS (in macaque monkeys), is a close genetic relation to HIV. Smith says that ‘...several different, but closely related, strains of SIV were developed for research purposes’ (Smith 2002:101 [my italics]). Simian AIDS was quickly recognised as providing, ‘the flexibility to test not only potential vaccines but also to test and verify theories of pathogenesis or immunological correlations with disease. Accordingly, there are a multitude of pathogenic and non-pathogenic viral strains that can be used in therapeutic and challenge studies to answer such questions as correlates of protection or progression to disease’ (Nath et al. 2000:429).

The SIV model was developed further when an SIV genome was engineered to carry a gene from an HIV isolate. These SIV/HIV chimera (hybrid viruses) became instruments known as SHIVs (Johnston 2000). SHIVs can replicate in macaques and can become highly pathogenic, capable of generating a lethal AIDS-like syndrome within a year (rather than the ten or so years often needed for HIV) (Girard et al. 2006). The use of multiple SIV ‘strains of differing virulence’ (Feinberg and Moore 2002:207) allows for a series of simplified testing conditions that can gradually become more complex.

The sheer variety of animal models that have been developed allow researchers to, firstly, adjust testing conditions for iterating between learning and relevance (e.g. by varying virulence, routes, dosages, and similarity between vaccination and challenge) and, secondly, examine different aspects of infection in turn (e.g. ‘R5’ and ‘X4’ tropisms).  

12 For example, one notable difference between SIV and HIV is when and which of the CCR5 and CXCR4 chemokine receptors the virus binds with (Nath et al. 2000; Girard et al. 2006). In about half of HIV infected humans, HIV that binds to CCR5 predominates early and throughout the asymptomatic phase, but a shift towards binding to CXCR4 is observed as these humans progress to AIDS. This shift in tropism to CXCR4 has not been
When primate models are used without coordination between research groups, commensurability between the results of testing becomes problematic. For example, ‘With the variety of challenge viruses and primates, comparison of one study to another is often not possible’ (Smith 2002:p107) and ‘These [SIV] species differ substantially. Since each of these SIV strains produced similar disease in a given macaque species and no macaque/ SIV model was clearly more relevant than another, researchers chose to study different SIV strains in different species of macaques. The resulting experiments, of course, often make direct comparison impossible. Additionally, researchers have now begun using SHIV as the challenge virus...’ (Smith 2002:p101).

To ensure that results between different groups are comparable requires a concomitant increase in the degree of coordination. The very factors that provide researchers with flexibility and the ability to adjust testing conditions incrementally would then need to be standardised and agreed for cumulative learning.

6 Variation within HIV vaccines

It is of course possible to persist with inventive effort in difficult domains, where pathogens are dangerous and animal models are not available. Under such conditions, the paths of development that can be taken are limited and variation within the vaccine options for a given disease is severely constrained. Note that vaccine innovation processes do not have binary outcomes (vaccine or no vaccine); options can vary in durability, breadth and type of protection as well as overall efficacy.

For HIV, the direction of inventive effort was forced away from the most common, tried-and-tested approaches to vaccine innovation as a direct result of the two variables highlighted in this paper. One consequence, as we shall see, is reported in SIV infected macaques (Johnston 2000). SHIVs provide an opportunity to take a controlled look at each of these tropisms in turn.
lower quality vaccines - which, counter-intuitively, are harder and costlier to develop through a testing regime. Any efficacy trial requires many volunteers, but if the vaccine is of a low efficacy then only very large studies will carry sufficient statistical power to be sensitive enough to detect efficacy of such vaccines. Similarly, if the vaccine does not have an immediate effect but may confer longer term benefits, like limiting disease progression, trials will need to track participants for that much longer.

6.1 From an HIV vaccine to an AIDS vaccine

Live and killed vaccines present a modified version of the whole virus to the immune system. Prior to 1980, all vaccines were made this way. A new approach was to present proteins, or subunits, from the virus. The subunit approach dominated HIV vaccine R&D (see for example, Gallo 2005:p178; Johnston and Fauci 2007). Since these vaccines feature only a small part of the virus, and crucially none of its genetic material, they can never cause the disease they are trying to prevent. Intuitively, they are safer, but they are also less likely to be effective because they present less of the virus to the immune system.

Concerns about killed-inactivated vaccines centred around the possibility that, as happened in the Cutter incident of 1955, the whole virus may not be killed properly during manufacture. Concerns about the live-attenuated approach were even more serious (Fischinger et al. 1985). Firstly, with such extreme variation, the weakened HIV could revert back to virulence. Designing a definitive test for measuring live vaccine safety is virtually impossible. Secondly, the weakened HIV virus might cause AIDS at a slower pace than the wild type virus with vaccinees developing AIDS thirty years after infection rather than ten years. To respond effectively to such a criticism would require testing for thirty years, and even then there is a good chance the result would be inconclusive. So for most

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13 If virus recovered from the victim resembled the wild type, one could suppose that it had replicated aggressively, and driven away the vaccine virus (wild type-induced disease). Alternatively, one could decide that the vaccine virus had changed to resemble the wild type and become virulent, thereby causing vaccine-induced disease. Either way, testing primary isolates would be unlikely to prove a vaccine guilty.
vaccine designers, killed and live vaccines were not viable, and the subunit approach was the only one left standing (Gallo 2005:p1894; Klein and Ho 2000:p309).

Limits to the subunit approach, and their cost implications, have become increasingly evident over the last twenty years. After gp120\(^{14}\) went to major clinical trials in 1999, its failure was clear, ‘The complete lack of efficacy... has been proven beyond any doubt’ (Girard et al. 2006:p4064). Another vaccine candidate underwent clinical trial but was abruptly halted in 2007, when it become clear that more people were being infected in the vaccine arm than in the placebo arm of the trial. The biggest clinical trial so far, involving about 16,000 people and costing $119m, tested a vaccine candidate that is essentially a combination of the two failed vaccine preparations discussed above, in a so-called prime-boost approach. In 2009, the results suggested some efficacy, but the effect was limited and transient.

The underwhelming clinical trial results give rise to three possible responses. Firstly, improve animal models and create new conditions for ‘testing as experimental intervention’.\(^{15}\) However, ”different groups are challenging with different viruses making it problematic to compare the relative efficacy of the vectors and immunization strategies” (Sekaly 2008: 10). The increase in varieties of models and techniques for using them puts more stress on research governance.

Secondly, consider initiating trials in humans more readily, in the ‘testing as validation’ tradition. However, this carries stubborn safety and cost implications. Less safe approaches (such as killed and live HIV vaccines) have not come anywhere near clinical trials, most likely because situations where such a risk

\(^{14}\) It was guessed that a large glycoprotein on HIV's surface, gp120, would be the most immunogenic part of the virus on which to base the subunit approach upon. It showed some early success in animal models but these successes needed to be interpreted with substantial caveats (e.g. weak strains and unusual routes were used for challenge).

\(^{15}\) Cats can be infected with feline versions of the virus. Mice can now be engineered to contain human lymphoid cells and receptor proteins, so called humanized mice (Denton and Garcia 2011).
would be tolerable are rare or non-existent. Situations where risky technologies are given as a last resort to the dying are not afforded to vaccines, because vaccines are usually given to the healthy. The safer subunit approach could be sent into clinical trials for every variant that results in the prospect of even a moderately effective vaccine, but as Dougherty (2007:p267) put it, “people working on drug discovery are figuring out the limits to blind search the hard way”. In short, this would become very expensive very quickly, at least after the first few attempts.

Thirdly, aim for lower quality. Since the early 2000s, expectations of an HIV vaccine started to get downgraded to a new perspective. 'It is unlikely that vaccine-induced immune responses will be able to prevent the establishment of [HIV] latency... A more realistic initial goal for HIV vaccine development is to dampen the initial viremia in an infected individual, maintain a low virus load, and prevent progression to AIDS’ (Graham 2002:208). Smith crystallises the shift, ‘vaccination, which may not affect the infection rate, may prevent disease' (Smith 2002:107). Preventing progression to disease, reducing transmission within the population, diminishing the spread of the epidemic; these fringe benefits become re-framed as more central virtues.

If an AIDS vaccine (rather than an HIV vaccine) were to reach clinical efficacy trials, there would be difficulties in setting an endpoint to the trial. The often long incubation period (decades) between infection and disease means that staging a trial with disease as the clinical endpoint would require more years and more people for the testing to be persuasive. Participant retention would be challenging and costly. Few tests exist to detect subtle but important changes in patients that may occur, so setting these endpoints may not be obvious. The

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16 Relinquishing the aim of preventing infection does not make curing AIDS any more likely. To prevent the ‘return’ of virus, any cells with the provirus integrated within the host genome, along with all of the copies of the cell after it was infected, would need to be identified and killed.

17 This assumes that the rate of new infections is constant. The length of the trial, the clinical endpoint chosen, the rate of new infections and the number of participants are four variables, which are all closely inter-related. Changing one directly impacts on the others.
complexities of the testing regime seem to shape the characteristics of the technology being tested, in this case prevention, delayed-onset of disease, symptom alleviation and reduced transmission.

6.2 Alternative trajectories

For HIV/AIDS, it is becoming apparent that antiviral cocktail drugs are extremely effective in reducing viral loads to undetectable levels, allowing patients to resume normal lives (Fauci et al 2014). Participants who become infected during a vaccine trial would need to be offered antiretroviral therapy (according to some ethical interpretations) but these therapies are expensive and would add to the cost of vaccine trials.

There are also important analytical consequences to such provision. If everyone who became infected during a vaccine trial quickly began taking antiretroviral drugs, it would be much trickier to tell whether the vaccine had delayed the disease. In such a setting, some of the vaccine’s potential benefits may go undetected. Even increasing the length or size of the trial may not clear up that kind of analytical problem. Thus, the development of highly active antiretroviral therapy (HAART) has served to increase the difference between ethical treatment conditions and effective learning conditions.

The development of HAART itself can be accommodated within our theoretical framework. HAART was not a sudden exogenous innovation, rather its development went through its own testing regime. Its trajectory may have suffered from a similar lack of animal models but crucially, it was able to access on-line clinical learning much more easily. AZT, for example, was one of the early antiretrovirals that carried highly toxic side effects. It was possible to develop and improve such drugs on-line in patients who were desperately ill, had few alternatives and were willing to tolerate non-efficacy as well as bouts of nausea, fatigue, kidney malfunctioning, lactic acid accumulation. In vaccine development, such symptoms would most likely prompt litigation. Thus, it was not long before the treatment trajectory was developed into HAART and hailed as a ‘game
changer’ (Gallagher 2015), with the familiar ritual of putting protagonists’ faces on the Time magazine cover (cf Jonas Salk, David Ho). Now that HAART conveys vaccine-like properties - preventing transmission and infection - preexposure prophylaxis HAART attracts the hopes and excitement normally associated with vaccine innovation (Volk et al 2015). The Economist magazine was even moved to ask if the ‘End of AIDS’ was imminent (well, if it is, it’s not thanks to a vaccine).

7 Variation between vaccines

It is not our intention for readers to interpret this paper as an a priori technical exposition of whether an HIV vaccine will be possible or not. The question of why it has been so hard to develop a vaccine against HIV AIDS, I have argued, can be answered in large part due to two variables: first, a combination of the lack of natural sterilising immunity and extreme variation, two factors which make the virus extremely dangerous; and second, the lack of suitable animal models. Moreover, these two variables have consigned vaccine efforts into a high-cost and low-quality trajectory.

The fact that HIV is an extreme outlier case with respect to both of these variables merely made them more salient, and facilitated their identification and characterization. However, when taken together with our theory, I can posit that these key variables influence the difficulty of the task of vaccine development against a range of other pathogens too.
7.1 Explaining variation in vaccine innovation

If the pathogen is too dangerous to learn on-line in humans, we can still learn offline in animal models before progressing to humans. But if the animal models are unavailable, and the pathogen is dangerous, we would expect vaccine innovation to be constrained. Figure 2 displays the two key variables in a matrix, and plots pathogen-caused diseases for which vaccines have been developed and not-yet-developed.

**Figure 2: Explaining variation in vaccine innovation through scope for learning**

<table>
<thead>
<tr>
<th></th>
<th>Have models been developed enough to learn ‘off-line’ in animals?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td><strong>4 The ‘Supply-elastic’ quadrant</strong></td>
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<tr>
<td></td>
<td>Influenza</td>
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<td></td>
<td>Tetanus</td>
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<td></td>
<td>Cholera</td>
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<td></td>
<td>Typhoid</td>
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<td></td>
<td>Strep pyogenes</td>
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<td></td>
<td><strong>2 The ‘Guts and Judgement’ quadrant</strong></td>
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<tr>
<td></td>
<td>Measles</td>
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<td></td>
<td>Mumps</td>
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<td></td>
<td>Rubella</td>
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<td></td>
<td>Adenovirus</td>
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<tr>
<td></td>
<td>Varicella-chickenpox</td>
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<td></td>
<td>Pertussis</td>
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<tr>
<td></td>
<td>No</td>
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<td></td>
<td><strong>3 The ‘Tentative’ quadrant</strong></td>
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<tr>
<td></td>
<td>Poliomyelitis</td>
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<td></td>
<td>Hepatitis A</td>
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<td></td>
<td>Hepatitis B</td>
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<td></td>
<td>Meningitis</td>
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<td></td>
<td>Diphtheria</td>
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<td>Yellow Fever</td>
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<td></td>
<td>Anthrax</td>
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<td></td>
<td>Rabies</td>
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<td></td>
<td>Human Papillomavirus</td>
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<tr>
<td></td>
<td>Rotavirus</td>
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<tr>
<td></td>
<td><strong>1 The ‘Difficult’ quadrant</strong></td>
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<tr>
<td></td>
<td>HIV (No NSI)</td>
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<tr>
<td></td>
<td>Tuberculosis (No NSI)</td>
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<tr>
<td></td>
<td>Malaria (No NSI)</td>
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<tr>
<td></td>
<td>Dengue Fever</td>
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<td></td>
<td>Gonorrhea</td>
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<td></td>
<td>Hepatitis C</td>
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<tr>
<td></td>
<td>EpsteinBarr-related diseases</td>
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<td></td>
<td>HerpesSimplex-related diseases</td>
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<tr>
<td></td>
<td>Shigella-related dysentery</td>
</tr>
<tr>
<td></td>
<td>Human Cytomegalovirus-related diseases</td>
</tr>
</tbody>
</table>

**Note on figure 2:** The yes/no answers in the matrix above misleadingly imply that these variables are dichotomous. They are not. They are continuous variables, wherein pathogens can be non-lethal but still cause serious morbidity and animal models can offer some but limited learning. NSI refers to natural sterilising immunity, expounded in section 5.1.

We see that quadrant one, which our theory predicts as being a ‘difficult’ quadrant, includes diseases for which vaccines have not been developed yet (e.g. HIV and Dengue Fever), as well as other diseases where vaccines are poor quality (e.g. tuberculosis and malaria).

In quadrant two, meaningful animal models were unavailable for measles, mumps, rubella, varicella and others. But on-line testing of vaccines could be
undertaken in humans by a ‘guts and judgment’ approach and with less reliance on animal models because these diseases are not usually life-threatening in their natural occurrence. If the matrix were not limited to vaccines, HAART would have been included in here too.

In quadrant three, our theory suggests vaccine innovation proceeds ‘tentatively’, because it is highly reliant on offline testing in animal models. Poliomyelitis, Hepatitis A and B, are potentially very dangerous, but it was possible to develop *in vitro* markers and correlates of immunity, and then develop through stepping stones for safety before initiating clinical investigations. The use of such animal models as stepping stones requires strong research governance because there are a variety of ways in which they can be used and interpreted, as well as a variety of models themselves (Yaqub and Nightingale 2012; Yaqub 2016).

Moreover, I have highlighted that animal models are not given and need to be actively developed. Diphtheria, poliomyelitis and yellow fever are all notable for transferring from the first difficult quadrant to the third tentative quadrant following the advent of new techniques and development of better animal models. Remarkably, upon transfer into the third quadrant, vaccines were developed for each of the respective diseases. Together with our theory, this provides additional reason to think that the technical difficulty of innovation is not necessarily fixed.

Lastly, quadrant four is perhaps most responsive to demand. The SARS and H1N1 influenza vaccines were developed extremely quickly, under auspicious circumstances, namely the fear of a global pandemic with potentially disastrous economic consequences. In contrast, typhoid vaccine remained largely undeveloped from its first iteration through to 1989, nearly a hundred years, presumably because rich countries had improved their sanitation systems. And it is tempting to think that a vaccine against streptococcus pyogenes might have been developed shortly after it was discovered in the 1930s, were it not for the fact that it is remarkably sensitive to penicillin and other antibiotics.
Figure 2 seems to explain much of the variation observed in vaccine innovation, which has hitherto gone largely unnoticed by economists.\(^{18}\) They have, thus far, tended to focus on incentives, conceding that technical opportunity may play a role, but making little effort to articulate what that technological opportunity might look like and ask whether it is important for theory and policy. The emphasis on incentives has given rise to some important classes of medical innovation that have attracted policy attention. Neglected diseases and vaccines, to name two such classes, attract concerns that market incentives are too weak. No doubt this is true for some within these classes (say, in the supply-elastic quadrant) but there exists vast variation in the difficulty of respective R&D tasks for others (say, across all four quadrants).

There is now a plethora of public private partnerships focused on product innovation which seem well situated to address market failures and weak incentives, but also seem to downplay the difficulty of the R&D tasks that lie ahead for some of them (Chataway et al 2010). One might view their presence in developing countries either as capacity-building programs that benefit the broader health R&D landscape (Chataway et al 2010:p1282) or, less charitably, as large distortions that draw resources away from other priorities whose combined burden and supply elasticity profile may make better investments (Moran et al 2009:p145).

Such arguments call for a rethinking of rationales for funding vaccine R&D compared to other options, especially in cases like HIV AIDS and dengue where 64% and 71% of their entire respective R&D budgets are spent on vaccines; this compares to 19% and 20% for other ‘difficult’ diseases like malaria and TB (Moran et al 2009:p141-3). More notably, R&D for typhoid and cholera vaccines, diseases in the ‘supply-elastic’ quadrant, are only 10% and 11% of their total R&D budgets (Moran et al 2013:p38).

\(^{18}\) The 31 diseases were selected at random and, in further research, other diseases could be added to the matrix and other product categories too (outside of vaccines). Diseases for which vaccines exist are surprisingly few in number; only 25 according to the US government [http://www.cdc.gov/vaccines/vpd-vac/vpd-list.htm](http://www.cdc.gov/vaccines/vpd-vac/vpd-list.htm) To account for 31 diseases represents a substantial portion of the vaccine sector and its activities.
Similarly, medical innovation in treatments is widely assumed to benefit from stronger incentives than in preventives (Dranove 1998; Kremer and Snyder 2015). But our paper has suggested that incentives alone are not a sufficient and complete explanation; treatments can often benefit from on-line clinical learning because patients are more willing to tolerate side effects and non-efficacy. With HAART treatment and HIV vaccine preventives, I found their testing regimes have contrasting effects on innovation.

7.2 Implications for policy and theory

In medical innovation, difficult R&D is when there is a risk to safety, and the lack of animal models substantially hampers knowledge accumulation. This makes innovation processes qualitatively distinct by increasing the number of ‘redesign cycles’ that must be explored. Our expectations about how easy it will be to develop products in difficult domains should be tempered, or our efforts increased, or both. Persisting with R&D in difficult domains, where trajectories are substantially constrained, may mean lower quality (in the case of HIV vaccine R&D, this could mean a vaccine of low-efficacy, low-durability, or low-breadth, if one at all). Moreover, and counter-intuitively, low quality vaccines are more expensive to test and develop.

Our central messages are more upbeat. Firstly, the difficulty of R&D is not fixed, it can be shifted through the development of models, instrumentalities and governance. A fruitful line of enquiry would be to combine analysis of how instrumentalities and models develop, together with an examination of how cognitive learning processes (e.g. Gavetti and Levinthal 2000; Kaplan and Tripsas 2008) interact with experimental design (Nightingale 2014; Dougherty 2015). To this end, the paper has shown that the testing regime framework can usefully contribute, and that broad units of analysis that focus on learning and knowledge accumulation are maybe more helpful than say, an exclusive focus on firms and their market positioning (see for example Kremer and Snyder’s (2006) explanation of why there is no AIDS vaccine).
Secondly, policy responses can and should consider alternatives throughout development. For diseases in the ‘difficult’ quadrant of figure 2, there are a number of non-pharmaceutical trajectories that could be pursued. None of these approaches are mutually exclusive, and they may need adaptation and development so that they work in concert with one another as part of a socio-technical system (e.g. HIV vaccine plus a microbicide, alongside preventive drugs for at risk populations). But for all of them, it seems worth exploring to what extent it will be possible to learn online and offline in order to better assess opportunity costs.

We seem to have increasingly sophisticated tools at hand for measuring demand (e.g. market analysis, burden of disease, DALYs, QALYs). Compared to these, measures of supply remain relatively underdeveloped. If asked about supply elasticity, we can rarely offer anything more insightful than “greater than zero but less than infinity” (Rosenberg 1974:p106). Much work remains to be done before supply measures can become as useful as demand measures, as part of a broader portfolio approach for policy makers deciding between alternatives (Wallace and Rafols 2015).

This paper has contributed to that agenda by focusing on vaccines. It suggests that for products going through elaborate testing regimes, as most do in medical innovation, (e.g. pharmaceuticals, devices), we would expect the two highlighted variables, the role of safety and experimental learning, to exert considerable influence over their innovation patterns. More generally across sectors, there may well be an array of variables at play, each sector having its own combination. It seems worth following in the tradition of earlier innovation

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19 For HIV, significant impact might be achieved through behavioural changes that reduce risk of exposure, including condoms, and needle exchange programs, together with broader changes in women’s rights and sex work. For malaria, antimalarial trajectories running alongside vaccine development echo the case of HIV, but here again there are alternative interventions in vector control, such as bed-nets and sanitation, that could be pursued. For TB, antibiotics, together with governance over how they are used, could offer hope beyond the existing low efficacy BCG vaccine - but for multi-drug resistant TB, one suspects that this strategy has run into diminishing returns and general changes in poverty-conditions are required (Farmer 1999).
scholars who have long pointed out structural sources of variation (such as capital-labour ratios and appropriability regimes by Pavitt, Teece and many others).

Somewhat uncomfortably, policymakers might need to come to terms with the idea that formal R&D is not equally effective across all quarters. Equally uncomfortably, researchers have a lot of empirical work to do in order to distinguish where it is that R&D might have its most powerful effects; for the ability to discern this is a highly interdisciplinary and sometimes qualitative endeavour, neither of which seems to be currently in vogue for much of the social sciences. Understanding what sorts of R&D contribute to what sorts of change could make a fundamental contribution to the ability of policymakers to shape the world we live in.

**Acknowledgements:**
I am deeply indebted to Richard Nelson and Paul Nightingale who have helped in more ways than I can appreciate. I thank participants of the Neglected Diseases workshop in Brazil in November 2015 and two SWPS reviewers for their encouragement and thoughtful comments. All remaining shortcomings lie solely with me. I acknowledge ESRC funding ES/L011409/1.

**References**


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20 It may be that some fields of endeavor are more amenable to formal R&D efforts than others. Mental health was recently found to have benefited from developments in practice much more than it did from formal R&D efforts over the last 20 years (Pollitt et al. 2013). The policy implications here could be to re-orient efforts towards more applied research and localised service delivery. For example, a UK public health program to ‘translate research into practice’ found that localised research collaborations (CLAHRCs) were not so much applying research as they were informing it with more relevant questions derived from local practice (Soper et al 2013). In education, a similarly beneficial-but-not-cheap program would be a hyper-local research system with every school or district having its own R&D or ‘evaluation’ department. Indeed, this could be happening informally but without the sanction of a fully resourced program in the way that CLAHRCs were, and below the radar of those who study and account for R&D efforts.


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