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# Variation in the dynamics and performance of industrial innovation: What can we learn from vaccines and HIV vaccines?

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## Abstract

This paper highlights two variables that we 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 vaccines, where the political economy of R&D appears to explain only part of the observed variation. We focus on HIV vaccine development and find that, together, these two variables not only make up a large part of how we would characterize 'difficulty' in the HIV R&D process, but they also seem to go a long way towards explaining why 33 other diseases have – or have not - had vaccines developed for them. If we persist in difficult R&D domains, development may be forced into trajectories that yield lower-quality products which, counter-intuitively, are costlier because they are harder to pass through clinical trials. Implications for theory and policy are discussed.

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*Keywords*: R&D strategy; R&D management; R&D trajectories; medical innovation; experimental models; vaccines; HIV AIDS.

## 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). Some sectors of the economy yield extremely rapid change (e.g. transportation, telecommunications, health) compared to others (e.g. education, crime) (von Tunzelmann et al 2008; Morlacchi and Martin 2009). Part of the variation is 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 has played an increasingly important role in economic growth and technical change over the last 150 years or so[1] (Mokyr 1990; Nightingale 2014:p13). Among industries experiencing particularly rapid change, we see deliberate and designed experiment feature prominently (Dougherty 2016). Even within a given sector, firms can experience substantially varying returns to their R&D investments depending, among other factors, on their choice of R&D trajectory and its management (Dosi 1982; Henderson and Cockburn 1994; Teece 2008).

This paper explores how R&D can lead to highly uneven effects on practice and how the cognitive and organisational conditions of knowledge growth can give rise to strikingly heterogeneous innovation outcomes. It examines contingencies and constraints in problem solving processes underlying technological change. The nature of these problem solving routines have profound effects on industrial dynamics, defining the possibility frontiers for technological paradigms and shaping the contours of technological trajectories within them, as highlighted carefully in a special issue of this journal (von Tunzelmann et al. 2008). Why some technological paradigms are more fruitful than others is an issue of central

[1] This ability seems to have temporal co-incidence with the kink in von Tunzelmann's Hockey Stick. Economic growth was roughly a flat handle of unchanging real income per capita until around 1800 when a rising blade of growth kicked in. McCloskey (2013) notes that neither historians studying the handle nor economists studying the blade provide a theory that fits both pieces of the hockey stick.

concern for policymakers and managers who make R&D resource allocations (Nelson 2008; Dougherty and Dunne 2012; Dunne and Dougherty 2016).

Biomedical research commands a high degree of shared appreciation for the role it plays in bringing about new medicines and their subsequent impact on medical practice and health (Sampat 2012; Dougherty 2016). However, medicine exhibits variation (Consoli et al. 2016). 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).[2] One might disregard some of the heterogeneity in medical innovation simply 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 R&D problems more or less tractable. The central questions of this paper might also be put forth as: what is 'difficulty' in R&D and how might this affect the performance of R&D trajectories?

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, and often people who have extremely low tolerance for anything that might be seen as jeopardising their safety (Yaqub

[2] 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 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.

et al 2014).[3] As to be expected, vaccines display heterogeneity too, some are developed quickly and others not at all (see figure 1). Clearly, figure 1 is not indicative of a sector undergoing overall increasing productivity in terms of the length of time needed for vaccine innovation. Even with repeated "breakthroughs" and "revolutions" in vaccinology, there remains substantial variation (Hilleman 2000; Plotkin 2005).

**Figure 1: High variation in the number of years to develop vaccines**

| Infectious Agent (disease) | Agent linked to disease | Vaccine licensed in U.S. | Years elapsed |
|---|---|---|---|
| *Influenzae* (influenza) | 1933 | 1938 (US Army), 1945 (US general) | 5 |
| *Measles virus* (measles) | 1953 | 1963 | 10 |
| *Salmonella Typhi* (typhoid fever) | 1884 | 1896 (British Army) 1914 (US general) | 12 |
| *Hepatitis B virus* (hepatitis) | 1965 | 1981 | 16 |
| *Rotavirus* (diarrheal disease) | 1973 | 2006 | 33 |
| *Bordetella pertussis* (whooping cough) | 1906 | 1948 | 42 |
| *Varicella zoster virus* (chickenpox) | 1953 | 1995 | 42 |
| *Poliovirus* (polio) | 1908 | 1955 | 47 |
| *HIV* (AIDS) | 1983 | Not yet | 32+ |
| *Human cytomegalovirus* (birth defects, mononucleosis) | 1960 | Not yet | 55+ |
| *Flaviviridae* (dengue fever) | 1907 | Not yet | 108+ |
| *Mycobacterium tuberculosis* (tuberculosis) | 1882 | 1927, but ineffective in tropical countries or children | 133+ |
| *Plasmodium spp.* (malaria) | 1880 | Not yet | 135+ |

A number of explanations have been put forward to explain variation in vaccine innovation, ranging from market failure to socio-political neglect. However, the

[3] 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.

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.[4] 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, we 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 we would define 'difficulty' in medical innovation. If such a definition is to serve even tentatively as a way to understand difficult R&D domains, the distribution of innovation outcomes across a given sector should reveal systematic differences according to these variables. Across HIV vaccines, and vaccines generally, we find that they do.

[4] Brusoni et al (2007) argue persuasively that PPPs should be seen less as corrections for market failure, and more as solutions to knowledge co-ordination challenges where a broker is needed to replace the role that large pharmaceutical firms often play (Brusoni and Geuna 2003). In the case of vaccines, this seems plausible and complementary to the explanation put forward here.

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). The first empirical section shows how HIV vaccine development in humans is extremely precarious, placing greater necessity and emphasis on animal models (section 4). The second empirical section shows how R&D difficulty constrains the array of trajectories available within HIV vaccines, and how persistence in the only trajectory remaining will have costly implications (section 5). Lastly, we discuss the extent to which variation in vaccines against other diseases can be explained using these two variables and explore this with some preliminary hypothesis testing (section 6).

The paper shows not only that difficult R&D trajectories can be defined and identified, but also what can be done to make such trajectories less difficult (that is, if one chooses not to adopt a strategy of identifying and avoiding such trajectories altogether).

## 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. This downplays the critical and underappreciated role of learning from other sources (Nelson et al. 2011). Technology can precede the scientific theories that explain why they work. Steam engines preceded thermodynamics, airplanes flew before aerodynamics, and transistors antedate solid-state physics (Yaqub and Nightingale 2012, Nightingale 2014). 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).

Technological knowledge, as distinct from applied science, has been described in engineering contexts such as aeronautics, chemicals, and electronics (Constant 1980, Vincenti 1990; Mowery and Rosenberg 1998; Rosenberg and Steinmueller 2013). There seems to be a similar corpus of knowledge for medical innovation, but this remains relatively underexplored (Consoli and Ramlogan 2012; Consoli et al. 2016; Yaqub 2016). Understating the role of technological knowledge may have contributed to unrealistic expectations of a biotechnology revolution; and now, the manifest failure of the revolution to materialise is prompting structural changes in the industry anew (Hopkins et al. 2007; Hopkins et al. 2013).

The growth of technological knowledge is important for industrial organisation because it serves to increase the endogeneity of science as well as redefine the productivity of the technological paradigm. The presence of such bodies of knowledge strengthens the incentives for private actors to invest in basic research, inspires confidence that future scientific research can be commercialised, and enhances the possibility of turning scientific research into marketable products and services (Rosenberg 1990; Rosenberg and Steinmueller 2013:p1152-55).

Accumulating technological knowledge 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 many other sectors of the economy, 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. Many 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 "off-line" (Nelson 2008; Sarewitz and Nelson 2008). Though in medical practice, the scope for improvements through actual practice is often severely constrained, and learning through off-line 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, off-line development serves first and foremost as a way to vicariously explore the safety of putative operational principles.

During off-line testing, we effectively move away from passive trial-and-error 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. As Dougherty (2007:p267) put it, "people working on drug discovery are figuring out the limits to blind search the hard way". 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, which can range from the highly purified to the more realistic. Simplifying assumptions can be gradually relaxed across a series of model organisms such as yeast and nematode worms through to zebra fish and mice. This generates a series of experimental stepping-stones, which trade-off ease of learning (simplicity) against clinical relevance (complexity) (Yaqub and Nightingale 2012:p2144; Nightingale 2014:p13-14).[6] The way such conditions

[5] See Brodie-Kolmer failures in Yaqub (2016).
[6] 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). They often serve to create completely new

are measured and controlled are an important part of the invisible organisational infrastructure that allows learning to emerge from abductive reasoning (Dougherty 2016).

Experimental models mediate between theory and practice (Morgan 1999), and have at least two other important characteristics that help form what Dougherty (2016) refers to as an infrastructure for emergence. Firstly, 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 management 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.[7] Secondly, 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 tools; then deploy them on everything in sight (Dougherty 2001; Baird 2004).[8]

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 prohibitively) expensive and can lock us into paradigms with less desirable

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phenomena (e.g. photoelectric, Zeeman, Compton effects were created in physics for theoretical learning) (Yaqub and Nightingale 2012:p2144; Nightingale 2014:p13-14).

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

[8] 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 validation 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).

performance characteristics (Dosi 1982; David 1985 Stirling 2008). Perhaps the analytical silver-lining to being locked in is that we can look ahead along certain trajectories to glimpse into their future.

## 3 Study design and limitations

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. We explore situations where the pathogen is dangerous (limiting learning in practice) and where stepping-stones are missing (limiting ability to move learning off-line). We infer about their importance from the extensive management processes that attempt to 'substitute for the missing prerequisites' (Gerschenkron 1962:p359).[9]

We strengthen within-case validity by considering how these two key variables affect different trajectories of development (variation *within* HIV vaccines), and also cross-case validity by considering how HIV vaccine efforts are different to other diseases (variation *between* vaccines). The HIV case was selected due to its high profile and R&D funding to help control for prominent rival explanations.[10] It is a deviant counter-theoretical case where key elements in the theory are missing, namely the ability to accumulate technological knowledge. The case of vaccines was selected on the assumption that this is a sector whose innovation patterns will readily exhibit the effects of safety concerns. The pathogens

[9] Hence, 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.

[10] Our case selection also addresses a paucity of empirical study of failure (Staudenmaier 1985; Denrell 2003), 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).

sampled for cross-case analysis were selected using two-stage stratified sampling (theoretical then random sampling).[11]

The study design is nested, such that we explore HIV as an example of vaccine innovation, and we then discuss vaccines as an example of medical innovation. The paper follows in a tradition of appreciative theorizing, using cases to illustrate and provide context to an explanation (Nelson and Winter 1982:p46). Weakness of generalizability can be mitigated if cases are linked with a theoretical framework. The analysis in this paper is therefore not based on extrapolating a pattern from cases. Instead, the cases are used to conjecture a falsifiable explanation about an important source of variation in medical innovation outcomes.

An important limitation of this paper's approach is that it does not attempt to model the entirety of vaccine innovation. The aim was to develop an explanation of parsimony and utility, one that follows the aphorism, "all models are wrong but some are useful", alert to what is importantly wrong, "it is inappropriate to be concerned about mice when there are tigers" (Box 1976:p792). As such, this should only be considered an initial positioning paper and a tentative first step towards understanding the role of these two variables in vaccine and medical innovation.

Our 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.

A particular strength of secondary data is the high reliability that comes from being able to revisit stable sources and interrogate them repeatedly whilst theory is being developed. Construct validity was strengthened using a

[11] Cases were selected to ensure coverage across our variables of interest, but then randomly from a list of pathogens published by the UK's Health and Safety Executive (HSE 2013) (see section 7).

triangulation approach with a varied range of sources and technical accuracy was corroborated with immunologists, biochemists, physicians, and others in the scientific community. Our training in biochemistry served well for navigating the technical literature.

The synthesised data was analysed using two forms of pattern matching to strengthen internal validity. In the first (HIV vaccines specifically), we took the outcome as given but focused on how and why the outcome occurred. In the second (vaccines in general), we sought to find a variety of outcomes that are consistent with an argument.

## 4 The HIV vaccine trajectory as an archetypal example of difficult R&D

This section explains why HIV vaccine innovation fits our theoretically-informed concept of difficult R&D. It explains why previous successes in vaccine innovation cannot be emulated against HIV. We see why learning on-line in humans is not possible, and how off-line development is hampered by the absence of animal models that offer suitable stepping stones. The objective here is not to trace the exploration of various dead-ends (which have been the source of much consternation and frustration) for the sake of historical record. Rather, by revealing the extensive efforts to substitute for missing stepping stones, we can learn much about how models and experiment are used in the innovation process more generally.

### 4.1 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. 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 plentiful. 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.

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 (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. 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. With HIV, there is little for vaccine designers to mimic.[12]

[12] Some rare individuals offer 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).

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). 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.

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.[13] 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 management.

### 4.2 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 animal species. Although HIV infects chimpanzees, it does not culminate in disease (AIDS) (Klein and Ho 2000; Nath et al. 2000).[14]

[13] 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).
[14] It replicates slower and does not gather in (and destroy) the lymph node architecture as quickly.

Reviews readily acknowledge that "we have no truly useful small animal model" and "the lack of a truly representative animal model" for HIV vaccine development (Gallo 1991:p1894; Klein and Ho 2000:p304). Yet, much of the HIV literature discusses data derived from animals. The inconsistency originates partly from passive observations on the state of animals as they exist naturally, and partly from the considerable effort expended in creating new effects through experimental intervention. Thus, Girard et al. (2006:p4066) intones more actively, "the difficulty [lies] in *developing* an appropriate animal model [our italics]."[15]

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).

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. So 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.

It is evident that researchers do not simply 'make the best of what they've got'.

[15] 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 such that they could become incorporated into an effective testing regime.

They intervene by tinkering and creating new effects. This can be illustrated by the two main models used in HIV vaccine development, SIV and SHIV in monkeys, which involve changing both the virus and the animal.

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 [our 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" (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).[16] When primate models are used without coordination between research groups, commensurability between the results of testing

[16] 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 reported in SIV infected macaques (Johnston 2000). SHIVs provide an opportunity to take a controlled look at each of these tropisms in turn.

becomes problematic. For example, since "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" (Smith 2002:p101).

To ensure that results between different groups are comparable requires a concomitant increase in co-ordination and management demands. 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.

## 5 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 severely constrained.

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 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.

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.

For most vaccine designers, killed and live trajectories were not viable, and the subunit approach was the only one left standing (Gallo 2005:p1894; Klein and Ho 2000:p309). 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.[17] 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.

Limits to the subunit approach, and their cost implications, have become increasingly evident over the last twenty years. After gp120[18] 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-

[17] 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.

[18] 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).

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'.[19] 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 management.

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 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 this would become very expensive very quickly.

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

[19] Cats can now 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).

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 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.

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 most 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. 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 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. It was not long before the treatment trajectory was developed into HAART and hailed as a "game changer" (Gallagher 2015).[20]

## 6 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, we 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. One might predict that an HIV vaccine either will not be developed in the near future, or if one is developed, it is likely to be a weak vaccine (which can of course still be useful). The implication is that alternative trajectories to vaccines may offer a more effective means for dealing with HIV.

When taken together with our theory, the evidence in sections 4 and 5 allows one to posit that these key variables influence the difficulty of vaccine innovation against a range of other pathogens too. This is a useful proposition to explore because systematic variation would suggest that vaccines may not offer an equally effective vehicle for social and technical change for *all* diseases. The pursuit of diverse trajectories that include non-vaccine options is needed not

[20] 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).

least because, for some diseases, non-vaccine trajectories can be turn out to be vital when it becomes evident that the vaccine trajectory is heavily constrained.[21]

This section also serves as a robustness check, providing reassurance that the case has not been cherry-picked to suit our argument. The counter-theoretical case is a way of dealing with the unobserved nature of the counterfactual. A world where HIV is safe to explore in humans or where HIV can be modelled easily in animals does not exist, so we cannot use more traditional methods. In order to evaluate potential outcomes (the difference between what happens and what would have happened regardless), we compare to other diseases.

### 6.1 Explaining variation in vaccine innovation

If the pathogen is too dangerous to learn on-line in humans, we can still learn off-line in animal models before progressing to humans. But if 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. The diseases were selected both theoretically (to ensure coverage across all four quadrants) and then randomly (from a list of pathogens).[22]

[21] 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).

[22] We used the list of biological agents compiled by the UK's Health and Safety Executive's advisory committee (HSE 2013). There a number of international classification schemes for micro-organisms based on their biological risks. The UK was the first to propose such a classification and, having been revised several times since 1975, is one of the most well established. We eschew their risk classifications because part of their consideration emerges from whether a vaccine exists, which would introduce endogeneity into our explanation. For our purposes, safe pathogens are ones that cause symptoms which normally clear (perhaps with routine treatment), and pathogens that model well in animals are ones that exhibit a similar disease pattern in humans and the animal(s).

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

| | | Have models been developed enough to learn 'off-line' in animals? | |
|---|---|---|---|
| | | Yes | No |
| Is the pathogen safe enough to learn 'on-line' in humans? | Yes | ***4 The 'Supply-elastic' quadrant***<br>Influenza<br>Tetanus<br>Cholera<br>Typhoid<br>Strep pyogenes-related sepsis | ***2 The 'Guts and Judgement' quadrant***<br>Measles<br>Mumps<br>Rubella<br>Adenovirus<br>Varicella-chickenpox<br>Pertussis |
| | No | ***3 The 'Tentative' quadrant***<br>Poliomyelitis<br>Hepatitis A<br>Hepatitis B<br>Meningitis<br>Diptheria<br>Yellow Fever<br>Anthrax<br>Rabies<br>Human Papillomavirus-related disease<br>Rotavirus-related disease<br>Chlamydia<br>Syphilis<br>Ebola | ***1 The 'Difficult' quadrant***<br>AIDS<br>Tuberculosis<br>Malaria<br>Dengue Fever<br>Gonorrhea<br>Hepatitis C<br>EpsteinBarr-related diseases<br>HerpesSimplex-related diseases<br>Shigella-related dysentery<br>Human Cytomegalovirus-related diseases |

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).[23]

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.

In quadrant three, our theory suggests vaccine innovation proceeds '*tentatively*', because it is highly reliant on off-line 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

[23] Whilst some might consider Ebola a difficult disease given its recent high profile coverage, it should be noted that several candidates had been found effective in animal primate models as early as 2000 (Jones et al. 2005).

stones for safety before initiating clinical investigations. The use of such animal models as stepping stones requires strong research management 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, we 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, or '*supply-elastic*'. 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. Similarly, antibiotics and strong diagnostics have probably dampened vaccine innovation efforts for syphilis and chlamydia in quadrant 3.

Figure 2 shows innovation outcomes for quadrant 1, where both variables take effect, are not good (no vaccine or low quality vaccine). In contrast, the other quadrants show better innovation outcomes, though there appears to be technology substitution effects in some cases. In figure 3, we re-tabulate to include innovation outcome frequencies. Note that we are not modelling innovation outcomes, we are asking whether the distribution of innovation outcomes is simply different from one quadrant to another.

**Figure 3: A contingency table of innovation outcomes from all four combinations of safety and modelling variables.**

| | Quadrant 1: *Difficult* | Quadrant 2: *Guts and Judgement* | Quadrant 3: *Tentative* | Quadrant 4: *Supply-elastic* | Σ |
|---|---|---|---|---|---|
| Yes, vaccine innovation | 0 | 6 | 10 | 4 | 20 |
| No, poor vaccine innovation | 10 | 0 | 3 | 1 | 14 |
| ∑ | 10 | 6 | 13 | 5 | 34 |
| Fisher's exact test (2-tailed) | p <0.001 | | | | |

The contingency table (figure 3) yields a very low p value (by Fisher's exact test), indicating that innovation outcomes across the quadrants are non-random and that further analysis may be fruitful.

> *$H_0$: All quadrants are produced from the same distribution of innovation outcomes.*
> *$H_1$: Some of the quadrants are produced from distinct distributions of innovation outcomes.*

For this, we compare one quadrant directly to another in all six possible combinations of quadrant pairs, as listed in figure 4.

**Figure 4: Pairwise Fisher's exact testing on all possible quadrant combinations**

| Quadrant combination | Fisher's exact test (2-tailed) |
|---|---|
| Q1:Q2 | p<0.001 |
| Q1:Q3 | p<0.001 |
| Q1:Q4 | p=0.004 |
| Q2:Q3 | p=0.517 |
| Q2:Q4 | p=0.455 |
| Q3:Q4 | p=1 |

Notably, all combinations that involve quadrant 1 yield very low p values, suggesting quadrant 1 is perhaps the most different from other quadrants in terms of innovation outcome distributions. This resonates with our theory that it is the two variables *together*, acting in concert with one another, that exert influence over the vaccine innovation process. For those wishing to build a fully

controlled logistic regression model to predict vaccine innovation, this suggests that the relationship is probably non-linear and that low pseudo-$R^2$ scores should not necessarily be dismissed as unworthy of further examination.

More formal hypothesis testing involved a number of assumptions, some of which were more unrealistic than others.[24] However, in combination with our qualitative analysis, we seem to be heading towards a consistent view.

Our safety and modelling variables appear to be important for explaining the variation observed in vaccine innovation, which has been ignored or unnoticed by most economists and policymakers. They have tended to focus on incentives, conceding that technical opportunity may play a role, with little articulation of what that technological opportunity might look like and reflection on whether it is important for theory and practice. The emphasis on incentives has given rise to some important classes of medical innovation that have attracted 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).[25]

The evidence in this paper suggests that rationales for funding vaccine R&D compared to other options bear rethinking. More strategic allocations for a given set of R&D resources might be made in cases like HIV AIDS and dengue where 64% and 71% of their entire respective R&D budgets are spent on vaccines; this

[24] We assumed all the observations are independent despite the fact that efforts against one disease is likely to have had benefits for other diseases. We assumed that our two explanatory variables are binary, despite the fact that pathogens can be non-lethal but still cause serious morbidity and animal models can offer some but limited learning. We also make the same assumption about our binary outcome variable despite the fact that vaccines can vary in durability, breadth and type of protection as well as overall efficacy.
[25] 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).

compares to 19% and 20% for other 'difficult' diseases like malaria and TB (Moran et al 2009:p141-3). There also appears to be potential to harvest lower hanging fruits in other cases. 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).

Similarly, medical innovation in treatments is widely assumed to benefit from stronger incentives than in preventives (Dranove 1998; Kremer and Snyder 2015). This is essentially where the rather cynical view - that pills are developed more readily than vaccines because they sell better - originates.[26] But this 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, we found the ability for their respective testing regimes to access on-line learning to have critical and contrasting effects on their innovation outcomes.

### 6.2 Implications for theory and practice

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

[26] Private companies find vaccines less financially rewarding than drugs. In 2001, the global marketplace for therapeutic drugs exceeded $300 billion, whereas worldwide vaccine sales were only about $5 billion . . . . It is not hard to understand why major pharmaceutical companies, capable of developing drugs and preventive vaccines, generally invest in drugs that patients must take every day rather than shots given only occasionally. Drug company executives have investors to answer to, after all. (Thomas, cited in Kremer and Snyder 2006:1).

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 management. 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 (Tripsas and Gavetti 2000; Kaplan and Tripsas 2008) interact with experimental design (Nightingale 2014; Dougherty and Dunne 2012; Dougherty 2016). To this end, the paper has shown that broad units of analysis that focus on learning capabilities and knowledge accumulation are helpful additions to approaches that take an exclusive focus on market positioning (see for example Kremer and Snyder's (2006) explanation of why there is no AIDS vaccine).

Secondly, being able to better identify difficult R&D domains might allow R&D strategy (in terms of R&D resource allocations) to consider alternatives more readily. 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 on-line and off-line in order to better assess opportunity costs.

Thirdly, the paper brings into question the nature of the constructed categories we use to describe and analyse industrial organisation. Even in science-intensive innovation, we see hierarchies that are not reductive through *Order, Family, Genus* and so on (Pavitt 1984; Nightingale 2008). There is little common essence between vaccine development and orthopedic surgery, yet both are loosely coupled together under the heading of medical innovation. This has important implications about how fine a level of industrial aggregation would be most useful for technology policy and analysis. As shown by seminal studies of the

typewriter, the dynamo, and the Britannia Bridge (David 1985; 1990; Rosenberg and Vincenti 1978), we should not shy away from "dirtying one's hands" with the details of technologies (Rosenberg 1976:p2), if one wants to develop an appreciation for their particular sources and consequences.

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 R&D managers and policymakers deciding between alternatives (Wallace and Rafols 2015).

The evidence in this paper is consistent with the idea that formal R&D is not equally effective across all quarters. A research agenda that distinguishes where it is that R&D might have its most powerful effects could turn out to be extremely useful for decision makers.

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