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Publication date

01-12-2012

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Citation for this work (American Psychological Association 7th edition)

Yaqub, O., & Nightingale, P. (2012). *Vaccine innovation, translational research and the management of knowledge accumulation* (Version 1). University of Sussex. <https://hdl.handle.net/10779/uos.23389829.v1>

Published in

Social Science and Medicine

Link to external publisher version

<https://doi.org/10.1016/j.socscimed.2012.07.023>

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Contents lists available at [SciVerse ScienceDirect](http://www.sciencedirect.com)

Social Science & Medicine

journal homepage: www.elsevier.com/locate/socscimed

Vaccine innovation, translational research and the management of knowledge accumulation

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Vaccines
Innovation
Poliomyelitis
Governance
Research translation

ABSTRACT

What does it take to translate research into socially beneficial technologies like vaccines? Current policy that focuses on expanding research or strengthening incentives overlooks how the supply and demand of innovation is mediated by problem-solving processes that generate knowledge which is often fragmented and only locally valid. This paper details some of the conditions that allow fragmented, local knowledge to accumulate through a series of structured steps from the artificial simplicity of the laboratory to the complexity of real world application. Poliomyelitis is used as an illustrative case to highlight the importance of experimental animal models and the extent of co-ordination that can be required if they are missing. Implications for the governance and management of current attempts to produce vaccines for HIV, TB and Malaria are discussed.

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Introduction

How is knowledge accumulated to generate socially beneficial technology? Vaccines, as a case in point, have arguably prevented more premature deaths, disability and suffering than any other medical intervention (Andre et al., 2008). However, vaccines are difficult to develop and can cost \$600 m–\$1 bn to bring to market (Douglas, 2004; NIH & NIAID, 2007; Plotkin, 2005). Even with investment, success is not guaranteed. HIV vaccine R&D increased to \$961 m in 2007, but most vaccinologists do not expect a vaccine in the next decade (Connor & Green, 2008). Other vaccines have eluded discovery for over a century despite investment (IAVI, 2008: 14), creating policy concerns about the rate of innovation.

Suggestions for ways to improve vaccine innovation have typically focused on upstream funding or downstream product acceptance. 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 (Blume, 2006), resistance to vaccine uptake (Blume, 2006; Mays et al., 2004; Nichter, 1995; Poltorak et al., 2005), the efficacy of promotion strategies (Blume & Tump, 2010; Pérez-Cuevas et al. 1999), delivery and access (Aston, 2001; IOM, 2003), industry norms (Blume, 1998), and social selection (Blume & Zanders, 2006).

Again, these explanations are all relatively silent on why vaccine innovation is so difficult. HIV vaccine research, for example, is well funded, has a lucrative market and is supported by a powerful coalition, yet vaccines are not forthcoming. Suggesting that some problems are simply ‘more difficult’ is unhelpful as it closes off analysis and suggests nothing can be done. In this paper we explore what makes innovation more or less difficult, as there is good reason to think ‘difficulty’ is not fixed. Innovations emerge from uncertain, path-dependent, socially distributed problem-solving processes (Dosi, 1982), so changing the processes can sometimes make previously intractable technical problems solvable. Hence, the pre-launch aspects of medical innovation are not just ‘technical’ problems addressed by scientists, and involve social questions about the relative costs of vaccines, or their implications for existing immunisation schedules, for example, that influence the cost, time and effectiveness of the process.

To explore if and how the difficulty of vaccine innovation can be changed, the Section 2 develops new theory to understand what influences the greater number of experimental cycles associated with ‘more difficult’ medical innovations. This suggests problem-solving is structured by, and moves across, a series of ‘intermediate conditions’ from the artificially simplified (and therefore unrealistic, low cost and low risk) experimental conditions that

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facilitate learning, to the realistic (and therefore complex, higher cost, and higher risk) conditions most relevant to practice. Understanding gained from simplified stages guides the design of increasingly realistic prototypes as the simplifying conditions are relaxed. As a result, the knowledge being generated undergoes qualitative changes as experiments' protection from social, regulatory, ethical and economic influences is removed. The seemingly purely technical, asocial nature of experiments is therefore the consequence of human action and not a reflection of its absence. This implies that the difficulty of innovation is influenced by researchers' ability to build manageable intermediate stages, as large jumps compromise experimental learning. This ability can be constrained by both biology and the social processes used to manage research. These points are illustrated in Section 3 by an historical review of poliomyelitis vaccine development. Section 4 discusses implications.

Experimental knowledge accumulation

The term "translational research" can be potentially misleading as the relationship between scientific research and innovation is more complex than the linear application of research it implies (Blume, 1998; Marincola, 2003). Technologies sometimes precede the scientific theories that explain why they work. Steam engines, planes and transistors, for example, existed before thermodynamics, aerodynamics or solid state physics were well developed (see Nelson et al., 2011 for medical examples). This is possible because technologies emerge from the 'operational principles' that define how they work (Vincenti, 1990: 209) which do not need a basis in science. It is possible, after all, to know how to produce an effect without knowing how an effect is produced.

Because these operational principles have the form 'phenomena x can be generated using y ', they generate more specific sub-problems (i.e. how to produce y) that iterate to produce a hierarchy of increasingly specific, inter-related problem-solving tasks (Constant, 1980: 24–27; Vincenti, 1990: 9). 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.

Since theory is a weak guide to practice, even after operational principles are discovered considerable operating experience may be needed to reliably understand their behaviour. Unfortunately, malfunctioning technology can be harmful and post-launch testing and modifications can be difficult and expensive (Nelson et al., 2011). It is therefore often desirable to know how a technology will work before it is launched, which requires considerable testing to identify, fine-tune and ensure the safety of different options (Constant, 1980). This is why many medical technologies undergo formal, regulated pre-launch testing.

An infinite number of possible explanations exist for any experimental results that occur during this testing, which might suggest learning is impossible. However, only a finite number of explanations are actually at hand, and scientific understanding can guide problem-solving by providing a context for interpreting results that helps researchers select a smaller sub-set that are reasonable to pursue. This helps reduce the number of dead-ends that are explored. Experiments can reduce the set of explanations further by creating purified conditions where only a subpopulation of competing explanations' assumptions hold (e.g. constant temperature, no light or oxygen, etc.). Experimenters intervene (Hacking, 1983) with instruments through varied, measured and controlled manipulation of experimental conditions (Nelson, 2008) to isolate and test specific mechanisms so the divergent implications of competing explanations can be compared, and effective operational principles discovered (Nightingale, 2004).

Innovation can therefore be constrained if the number of possible explanations is too large, at a given level of understanding, to select from at reasonable cost, and simplified experimental conditions are too unrealistic to usefully learn from. This can be addressed by initially building up understanding from simplified models and then gradually relaxing simplifying assumptions to make experiments more realistic. This generates a series of experimental stepping stones in the path from laboratory experiments to working products. Biologists use a number of standardised 'model organisms' from yeast, through nematode worms, to zebra fish, mice and monkeys, before human trials that allow them to select settings that trade-off ease of learning (simplicity) against clinical relevance (complexity). This is why animal models are so central to medical research (see Leydesdorff et al., in preparation, Fig. 1).

When using these models two styles of testing are used. Passive 'testing as validation' involves testing whether similar problems have similar solutions (Nightingale, 2004). This can be largely a-theoretical because it is not necessary to know how a technology works in order to know that it does work. However, it offers little guidance about what to do if tests fail. In such cases, rather than a cycle of conjecture and refutation, active 'testing as experimental intervention' is used to build artificial experimental conditions that create phenomena to allow theoretical learning (Hacking, 1983). The photoelectric, Zeeman, Compton, and Josephson effects in physics, for example, came into being through human ingenuity to support theoretical learning (Hacking, 1983).

Since new phenomena are being created in these experimental settings, variations in local experimental practice, instruments, and protocols can make comparison difficult. Comparing two different vaccines using virus types of varying pathogenicity, administered by different routes of infection, in different amounts, using different animal models and end points, might be meaningless (Yaqub, 2008). This is a particular problem with biomedical research where scientific knowledge often has only local application because, unlike the purified settings of a physics experiment, in biological settings multiple 'laws of nature' interact in complex, non-linear ways (West & Nightingale, 2009). The knowledge that is produced can therefore be specific to the experimental conditions, so that experimental reproduction requires considerable 'tinkering' and tacit knowledge (Baird, 2004; Fleck, 1981; Fujimura, 1992). This makes the co-ordination of the distributed research groups working on complex technologies difficult, so that bio-scientific advances can take decades to reach clinical application (Hopkins et al., 2007).

Because knowledge may not necessarily integrate readily, testing often requires standardisation, management, and co-ordination to create comparability between experiments and ensure fragmented knowledge accumulates through the stages and cross-sectionally across different groups working in parallel. Hence the difficulty of innovation isn't fixed and can be reduced if effective research governance can reduce the number of costly and time consuming experimental cycles that are required to generate a safe and effective product. When this co-ordination is not in place knowledge accumulation can be constrained, even if additional research funding is provided or demand is increased.

Research design

To illustrate the importance of an effective testing regime for vaccine innovation, we use a deviant (or extreme outlier) counter-theoretical case where a key element in the theory is missing. The theory suggests that innovation moves across a series of stepping stones, and we explore a situation where early stepping stones are missing (because the virus does not infect small mammals). We infer about their importance from the extensive governance

processes that 'substitute for the missing prerequisites' (Gerschenkron, 1962: 359). To increase within-case validity we use three internal cases and discuss between-case validity in relation to malaria, tuberculosis and HIV (where animal models are also missing) in the conclusion.

The data and analysis are structured based on Blume's (1992) 'career' framework (Hopkins, 2004) that links to research on clinical trials, community dialogue (Bastien, 1995), immunisation schedules, health systems (Bonu et al., 2003), and funding and production mechanisms (Bryder, 1999). Our data draws on a range of historical sources, including practitioners' accounts, scientific reviews and journals, histories, biographies, policy reports, newspaper articles, and publications by NGOs such as advocacy groups, charities and foundations. This research was subject to the University of Sussex's ethical review.

The path to poliomyelitis vaccines

Vaccine innovation starts with diagnosis, whereby previously unrelated symptoms are grouped as a disease, around a disease-causing pathogen (Rosenberg, 2002). Understanding disease mechanisms (pathogenesis) clarifies the problem, helps both define the operational principles needed to address the disease, and generate the collective vision and shared expectations which mobilise social, financial and political resources within networks as 'opportunities presented as promises, get accepted and become part of an agenda; and are subsequently converted into requirements that guide search processes' (Blume, 1992: 64–70; van Lente, 1993: 198).

With poliomyelitis this occurred in the middle of the 19th century after physicians associated paralysis with inflammation (*itis*) of the grey (*polios*) matter of the spinal cord (*myelos*) of children. Initially, associated with teething, the clustering of cases in households suggested an infectious disease (Carter, 1965: 8). This was shown in 1908 when Landsteiner and Popper infected monkeys by inoculating their brains with infected human spinal cord tissue (Robbins, 2004: 17). The following year, Flexner and Lewis passed the infection between monkeys (Carter, 1965: 9) starting the search for the infectious agent (Mullan, 1989: 100).

Since infectious disease agents can be poisoned (with drugs) or killed by an immune system (primed by vaccines) this diagnosis added a new potential option for treatment to public health strategies, which moved away from environmental improvement and quarantine towards prophylactic vaccine development (Baldwin, 1999; Hortsmann, 1985; Tomes, 1990). However, the exact operational principle remained unclear without further investigation of poliovirus' epidemiology.

By 1910 it was demonstrated that monkeys surviving poliomyelitis resisted re-infection and their blood contained a substance that neutralised the virus (Paul, 1971: 108). Since vaccines' operational principles are conditional on infection conferring immunity, this was a major 'proof of concept' finding. As a result, in 1911 Flexner issued a press release predicting a remedy within six months (Paul, 1971: 116; 125). However, several obstacles remained. Laboratory diagnosis was dependent on testing spinal fluid, obtained through a specialised, painful and dangerous procedure, with the result that serum was scarce and unreliable (Rogers, 1992). Vaccines' operational principles depend on safely stimulating an immune response by manipulating and developing the virus to limit pathogenic (disease causing) qualities, while accentuating immunogenic (immune-response stimulation) qualities. In general, the more pathogen there is, the larger number of substances and techniques that alter the pathogen can be explored to determine whether the changes produce a 'safe' and 'appropriate' response. It was quickly recognised that the lack of sufficient wild-type virus was

a significant barrier to understanding poliomyelitis pathogenesis and developing a vaccine (Robbins, 2004: 17).

It is now known that three types of poliovirus can enter the mouth and nose in saliva droplets or microscopic faeces and then reproduce in the gut. Normally the immune system limits infection, but in 1–2% of cases the virus travels through the blood into the central nervous system, causing meningitis and paralysis (Racaniello, 2006). The model postulated by Flexner in 1913 was different (Rogers, 1992) and suggested poliomyelitis travelled through the sinuses to the brain and spine, and grew in nervous tissue. These assumptions led researchers down three dead ends. First, they tried to culture the virus in nervous tissue. Second, they reasoned that vaccines would not work because poliovirus did not enter the bloodstream. Third, they were unaware they were dealing with multiple types of virus, which made comparing experimental results across and within laboratories difficult. As a result, the consensus of the scientific community from 1913 till 1935 was that a vaccine was possible but unlikely (Carter, 1965: 58; Paul, 1971: 113).

By 1916, the annual incidence of paralytic poliomyelitis in the US was over 27,000, killing more than 7000. Reported cases had never exceeded 7.9 per 100,000 before, but in 1916 the rate jumped to 28.5 per 100,000 (Paul, 1971: 148; Rogers, 1992: 10). Hospitals refused to admit new cases, cities began insect control programmes and impounded cats and dogs (Paul, 1971: 291) and parents sealed windows and refused to let children play outside (Oshinsky, 2005).

When Franklin Roosevelt was struck by poliomyelitis in 1921, his carefully handled public relations altered perceptions of disability and helped structure networks of resources for scientific research (Gallagher, 1985; Oshinsky, 2005). When it was reported in 1924 that he bathed in Warm Springs Georgia, other sufferers followed. Roosevelt then spent two thirds of his personal fortune turning it into the Warm Springs Foundation under the direction of his former law partner, Basil O'Connor, whose daughter later died from poliomyelitis (Oshinsky, 2005).

In 1934 Roosevelt staged nationwide charity balls 'to dance so others may walk' (Carter, 1965: 14) to relieve Warm Springs' debts (Rose, 2003). Despite the stock market crash the campaign raised \$1 m that year, \$0.75 m the next, and reserved \$100,000 to 'stimulate and further the meritorious work being done in the field of infantile paralysis' (Carter, 1965: 14–18). The first sixteen research grants totalled \$250,000, one of which, for \$65,000, was distributed to Maurice Brodie (Benison, 1967: 179).

Brodie–Kolmer vaccine failures

The optimism of the time was based on the successes of tetanus and diphtheria vaccines, which had saved millions of lives by 1910 (Chase, 1982: 302). They were based on passive immunisation, using sera drawn from the blood of immunised horses. Flexner and Lewis attempted to replicate this approach but reported 'failure to produce neutralising serum in the horse... [it] displayed no power whatever to inhibit the action of the virus' (Chase, 1982). Poliovirus could not be grown in horses, or any other non-primate. Further research therefore required either humans or monkeys – 'cranky, expensive creatures, which (prior to antibiotics) had a way of succumbing to other diseases before the researcher could measure its responses to poliomyelitis. No laboratory combined sufficient interest with enough funds to maintain all the monkeys needed for thorough study of poliovirus' (Carter, 1965: 19).

Had it been possible to infect mice or rats, they could be used as cheap, fast and simple animal models to generate experimental data on infection (Nightingale, 2000). Since this was not possible innovation took a path of 'testing as validation'. In 1936, two rival investigators independently conducted field trials of vaccines (Chase, 1982; Robbins, 2004). Brodie and Park used a formalin-

treated preparation of mashed up infected monkey spinal cord (i.e. a killed virus approach), whilst Kolmer used 'a veritable witches' brew' (Paul, 1971: 258) of live virus made from spinal cords treated with chemicals and refrigeration. The two teams hurried their vaccines into trials. Many of the 12,000 children Kolmer vaccinated were killed or paralysed, which sparked a two decades 'wave of revulsion against human vaccination' (Paul, 1971: 260).

The trials were indicative of the community's testing norms (Constant, 1980: 8). Vaccinology was seen as an empirical science that did not require knowledge of how a vaccine worked. Smallpox and rabies vaccines had been developed without formal identification of their infectious agents. This approach works if new vaccines follow the same operational principles and pass validation tests. But failures provide no additional insight. As the theory section highlighted this requires a different style of testing and a more sophisticated testing regime.

In hindsight, testing in this case was impeded in three ways. First, feedback loops in learning cycles were weak because so little virus was available. Few researchers could diagnose infection quickly by extracting spinal fluid, so most researchers had to wait for symptoms when testing for any immunity. Second, experimental iterations and refinements could not be made cheaply, easily, or quickly because of the lack of a simple model. Monkeys are difficult, slow and expensive to work with. Brodie only tested his vaccine on 20 monkeys before testing 300 children whilst Kolmer tested a few monkeys, himself, his children and 22 others before distributing his vaccine (Paul, 1971). Thirdly, the community did not establish the types of poliomyelitis virus they were working with before trialling. Each issue needed to be addressed.

The failures moved Roosevelt to abandon the Birthdays Balls after 1937 and rename the Warm Springs Foundation the National Foundation for Infantile Paralysis (Rose, 2003). Its mission was to 'ensure that every possible research agency in the country is adequately financed to carry out investigations into the cause of infantile paralysis and the methods by which it may be prevented' (Carter, 1965: 15). Significantly, it would also 'lead, direct, and unify the fight of every phase of this sickness' (Markel, 2005: 1408).

Radio promotion raised over \$1.8 m in a week, with proceeds increasing so that by 1945 receipts totalled \$18 m, and by 1955 \$67 m (Carter, 1965: 26). Between 1938 and 1962, the Foundation's overall income was \$630 m with \$69 m spent on vaccine R&D (Paul, 1971: 312). In 1947, Harry Weaver was appointed as Director of Research to manage the research effort. He invited leading researchers to conferences, published proceedings (Smith, 1990) and instituted round table discussions to 'encourage communication and intellectual cross-fertilisation in a field notable for its lack of both' (Carter, 1965: 57). These led Weaver to the view that whilst undirected researchers establish more certainties about a disease, they often investigated questions of little technological relevance. He wrote to O'Connor:

"Only an appalling few...were really trying to solve the problem of poliomyelitisIf real progress were to be made, more exact methods of research would have to be clearly defined, procedures and techniques would have to be developed ... individual groups would have to sacrifice ... their inherent right to roam the field, and concentrate their energies on one, or at most, a few objectives" (Carter, 1965: 57).

Previously the Foundation funded investigator-initiated projects (Benison, 1967; Smith, 1990), but Weaver set up a Scientific Research Committee to more carefully direct and co-ordinate research. Its head, Dr. Thomas Rivers, noted:

"... the Scientific Research Committee received any number of applications from individual investigators and, while many were

worthwhile in themselves, together they did not seem to be going anywhere. They were too haphazard for a program and I thought that the Foundation would be better served if a committee surveyed the field and blocked out problems that needed solution... the committee should seek out the men and institutions capable of researching such problems and support them" (Benison, 1967: 231).

Despite resistance, Rivers and Weaver directed an 11 point research plan that tackled the three impediments to vaccine development directly (Benison, 1967: 229). After Weaver complained that experiments were 'botched by scientists who used too few monkeys or made the error of reusing monkeys whose systems were misleadingly immune to another type of the virus' O'Connor resolved to 'go into the monkey business' (Carter, 1965: 73).

Establishing Okatie farms

As noted previously, after decades of trying, researchers had not infected small, inexpensive laboratory animals. Since economies of scale in experimentation, unlike production, typically depend on reductions in size (Nightingale, 2000) this substantially constrained research. While monkeys could be infected they required specialised care and quarters (Paul, 1971: 101). Researchers had to spend significant proportions of their time arranging their housing and feeding, and 'placating the assistants who had to work with them' (Smith, 1990: 123). Skilled technicians were needed to clean, feed, look after, and handle the monkeys whilst contending with the risk of bites, thumps and disease.

Despite these difficulties, demand outstripped supply as capturing wild monkeys was difficult. Cynomolgous monkeys provided good disease models and were easier to work with, but they were scarce and expensive to import from the Philippines and Indonesia (Smith, 1990; Time, 1954). Rhesus monkeys were more abundant in India, but are sacred to Hindus. Researchers complained that their monkeys arrived dead or diseased (see Salk's correspondence in Carter, 1965: 75).

To address these problems O'Connor established Okatie Farms while Weaver organised monkey 'airlifts' from India and Indonesia (Time, 1954: 7). At the Farms monkeys recuperated before being dispatched to laboratories, saving laboratory time, effort and space. Smith (1990: 121) describes the Farms as 'a rehabilitation facility that was also a centre for research in the solution of problems nobody else much cared about.' The Farms developed carefully formulated dry monkey-feed (Carter, 1965: 76) and provided instructions on feeding (Smith, 1990: 122). The historical record contains long correspondences regarding the minutiae of delivering, feeding, handling and disposing of monkeys (Carter, 1965). This 'monkey business' substantially lowered the costs, improved the quality and raised the comparability of experimentation. Once the monkeys were in place the next barrier could be addressed.

Tissue culturing

The effort to develop better methods for propagating the virus continued unsuccessfully throughout the 1930s (Robbins, 2004). By 1940 two groups grew poliovirus in human embryonic brain tissue, but did not extend the technique to non-nervous system tissues (Burnet & Jackson, 1940; Sabin & Olitsky, 1936). Robbins (2004) suggests this delayed the vaccine by almost a decade.

This reflected the orthodoxy that poliovirus was a nervous system virus, which occasionally spilled over into the blood. Unfortunately the finding that the virus could grow in brain tissue only reinforced the notion that poliovirus was neurotropic. It was therefore thought that a vaccine was dangerously impractical

because it was impossible to remove all the monkey-nerve cells during preparation, raising the risk of fatal encephalitis (Rogers, 1992).

However, Paul and Trask discovered the virus in human faeces, implying it could reproduce in the alimentary tract (Paul, 1971: 281). In 1940, Bodian and Howe infected chimpanzees by feeding them and in 1947 Melnick and Hortsman demonstrated the animals' resistance to re-infection (Paul, 1971: 287), strongly indicating an intestinal infection.

The Foundation commissioned several groups working on culturing techniques and supplied them with poliovirus and funding (Carter, 1965: 60; Chase, 1982: 292). The Foundation also helped source embryonic tissue from local maternity hospitals and proactively dealt with the qualitatively different social concerns that arose from experiments with human tissues derived from the foreskins of newborn boys, placentas, miscarriages and still-born tissue (Smith, 1990). A major breakthrough came when Enders, Weller and Robbins succeeded in cultivating poliovirus in human non-nervous tissues (embryonic skin muscle). Soon poliomyelitis was propagated in variety of tissues (Robbins, 2004: 18).

While initially underappreciated (Paul, 1971: 373), tissue culture transformed testing by providing a safer and simpler experimental environment, tighter feedback loops and faster testing cycles, so that experimental knowledge could accumulate faster. It drastically reduced the need to import monkeys which saved money and time. As Chase (1982: 286) notes 'worse than the costs of buying and maintaining these animals were the temporal limits they placed on the investigative progress'. With the need for experimental animals vastly reduced, more ideas could be tested, costs reduced, feedback loops shortened, and results could be assessed more quickly (Nightingale, 2000).

Tissue culturing also provided better quality virus that was relatively free of protein and, crucially, free of encephalitis causing nerve cells (Robbins, 2004: 18). This reopened a previously closed operational principle. The Foundation exploited the breakthrough by educating specialists and training technicians so the technique would diffuse quickly, and continue to be developed (Carter, 1965: 26). This 'tinkering' knowledge is important because to achieve good yields, cultures have to be kept at precise temperatures, in very clean containers, of the right shape and size, with the right kind of lids and stoppers (Smith, 1990). The technique was improved in 1953, when human embryonic tissue was substituted with the testicles or kidneys of monkeys generating a substantial economy of scale. A single testicle or kidney could provide enough tissue culture for two hundred test tubes when the previous method generated enough for one (Carter, 1965: 114).

Finally, tissue cultures could be used to establish shared standards. Since infected cells were rapidly destroyed (Chase, 1982: 292; Robbins, 2004: 19) the cytopathic effect could indicate viral replication and the presence of viruses. With some technical modifications, tissue cultures were also used for virus titration, antibody quantification, virus isolation from clinical specimens and antigenic typing of virus isolates (Robbins, 2004: 19).

These improvements allowed research groups to compare their results, which then revealed new paradoxes as similar experiments were producing different results. As Robbins (2004: 18) reflects, small differences in how long or how often nutrient media were changed were enough to produce opposite results. Rivers sought to find flaws in earlier research to explain the different results (Carter, 1965: 90) but realised that different research groups were using different viruses. Sabin and Olitsky experiments had failed because their MV virus was the only poliovirus that would not grow in non-nervous tissue. Rivers noted if they 'had worked with another strain... the chances are that... we would have had a breakthrough' much earlier (Carter, 1965: 91). Working without a clear catalogue

of the various poliomyelitis strains had impeded vaccine development because the scientific facts that were established were local to particular virus types which made comparisons difficult.

Virus typing: a 'dull and menial' program

In 1948, Weaver pushed virus typing as an important, but theoretically unexciting, strategic research project. For a long time it was suspected that multiple strains of poliovirus existed but to establish this would involve a longer systematic effort that would involve substantial investments in laboratory space, monkeys, technical personnel, and equipment. Much like the Human Genome Project senior researchers were reluctant to take on the 'drudgery' of several years of mechanical and boring work (Carter, 1965: 61).

Immunological testing was difficult, imprecise and time consuming. A group of monkeys was infected with a strain of poliovirus, say Type I virus, and allowed to recover. If they got sick when challenged with 'standard' doses of an unknown virus, one infers a new strain, say Type II, is present. This strain can then be injected into another group of monkeys that have recovered from Type II virus infection. If they remain healthy, the unknown strain can be confirmed as Type II. If they get sick the procedure is repeated.

The whole protocol, even when executed perfectly and with a lot of luck, would have required many monkeys. But there are many inaccuracies in making the deductions. Preparing 'standard' challenge stocks is a delicate, time consuming and frustrating job because viruses differed in their pathogenicity and infectivity. As a result, the standard dose was different for each virus strain and could be miscalculated easily. When challenge stocks are too weak, very mild infection can be mistaken for prior immunity. When they are too strong the monkeys end up dead. To guard against such miscalculations, each step of the process needed to be repeated with dozens of monkey groups (Smith, 1990). Only then can a public challenge-stock database be compiled and shared.

Weaver initially set up an eminent advisory committee to lead the project but they were uninspired. Jonas Salk, who was to develop a working vaccine, had just set up a new laboratory of his own after having worked on a formalin-inactivated influenza vaccine with his mentor, Thomas Francis, for the US Armed Forces (Carter, 1965: 35; Galambos & Sewell, 1995: 47). Salk was looking for his laboratory's first grant when he was encouraged to take on the work being offered by the Foundation (Carter, 1965). It was seen by Salk as 'a dull but dependable investment that would provide a regular dividend of money' (Smith, 1990: 110–117).

The large scale experiment spanned four universities and two years, acquired and classified over 200 clinical strains of poliovirus, cost \$1.37 m and used 30,000 monkeys imported at great expense (Chase, 1982). To put this in perspective, only 17,500 monkeys had been used in all previous experiments (Carter, 1965; Chase, 1982) and in 2002 only 52,000 non-human primates were used across the entire US R&D system (USDA, 2002). The project showed conclusively that there were three, and only three, immunologically distinct types of poliomyelitis virus (Bodian, 1949; Time, 1953). This crucial information provided a standard against which future vaccine candidates could be compared (Carter, 1965: 275). The Foundation then funded expensive epidemiological studies to establish where the three strains were prevalent, which informed decisions about the location of future field trials.

Discussion and conclusion

This history of poliomyelitis vaccine development has hopefully shown the difficulty of medical innovation isn't necessarily fixed. Pre-launch, technical features of vaccine development can be

explored using Blume's (1992) framework as testing moves across a series of stages from the protected, simplified, low cost and low risk conditions of the laboratory, to the social complexity of a high risk and high cost vaccination programme.

After the initial problematisation and diagnosis of poliomyelitis, simple extrapolation of an older operational principle produced disastrous results, and shifted the research agenda towards a new approach based on understanding disease pathology. As with many medical technologies, human safety concerns were paramount and shaped how this approach was undertaken. The absence of an animal model made experimentation more costly, time consuming and difficult. As a result, extensive research governance was required to substitute for the missing animal models. These interventions included: the provision of monkeys to reduce the costs of experiments; the development of tissue culture techniques (to provide more consistent experimental inputs, with faster, tighter and better defined experimental cycles); and the establishment of an expensive virus typing programme to clarify a scientifically dull but technically important question.

Once this was done, the final 'stepping stones' involved discovering how much antibody stimulation was needed to acquire immunity (Yaqub, 2008) and then testing in humans. Three kinds of vaccine went through clinical trials, each based on a different operational principle: passive antibody immunisation, and killed and live poliovirus immunisation. They yielded a killed vaccine in 1955 (Markel, 2005), and a live vaccine shortly afterwards (Robbins, 2004) which have succeeded in bringing poliomyelitis close to eradication (Blume, 2005). The subsequent development of genetically modified animal models has made their improvement much easier (Ren et al., 1990).

The theory behind this history suggests that medical innovation is likely to be constrained in similar 'difficult' experimental situations where there are gaps between experimental stages. Under such conditions, research may need more active management to ensure knowledge can be shared, generalised and accumulated. However, care must be taken when generalising from this history as it occurred just after Enders' breakthrough in tissue culturing, when extra co-ordination would be particularly valuable.

All the same, the lessons it offers may have relevance today because three major diseases – HIV, tuberculosis and malaria – also have missing intermediate stages and further complicating factors (see Table 1). With most vaccines, either the disease is safe enough to

allow volunteers to be used if no animal models exist (e.g., measles, mumps, rubella, human adenovirus and varicella), or the disease is fatal and an animal model exists (e.g., hepatitis A and B). For poliomyelitis, HIV and malaria, and to a lesser extent tuberculosis, the disease is fatal and animal models are problematic.

Vaccine development is further complicated because there is no natural sterilising immunity for these diseases. Since the body does not clear these pathogens, the normal operational principle of generating sterilising immunity without causing disease is not available, and a different operational principle is needed. Furthermore, these pathogens show either high or extreme genetic variation (HIV infection can quickly generate many quasi-species within a single individual). This means that vaccines have to work quickly (perhaps within hours of infection) to effectively neutralise all variants. Moreover, it closes off the use of attenuated live vaccines that might mutate back into a deadly form.

Given these additional complications, the lack of early stage animal models would be expected to substantially hamper knowledge accumulation, which makes their innovation processes qualitatively more difficult by substantially increasing the number of 'redesign cycles' that must be explored. This suggests that our expectations about how easy it will be to produce a vaccine should be tempered, or our efforts increased, or both. Moreover, it helps explain the high profile failures in HIV vaccine innovation, thus far, the long time it is taking to generate a Malaria vaccine, and why no new TB vaccines have been successful since BCG was introduced in the 1920s, despite BCG's limited effectiveness.

The key argument of this paper is more positive: while these biological features of vaccine development change the number of redesign cycles and dead-ends that are explored, they do not fix them. Improved research governance and management have the potential to reduce them. However, it is unclear if recent changes will improve this co-ordination. The biggest recent change has been the rise of global, disease-specific Public Private Partnerships (PPPs), such as the International AIDS Vaccine Initiative (IAVI) and the Malaria Vaccine Initiative (MVI). Whilst these organisations have played important roles in increasing funding (McCoy et al., 2009), many are based on a social venture capital model which, like commercial venture capital, works best after the knowledge accumulation problems highlighted in this paper have been solved. Few PPPs have the Foundation's ability to direct research, and while private sector actors brings benefits, their increased use of

Table 1
Qualities of pathogen affecting learning during vaccine innovation.

	Polio	HIV	TB	Malaria
Infectious, allowing a vision of a vaccine to be formed	Yes Oral transmission (non-mucosal), free virus (Racaniello, 2006)	Yes, complex transmission by virus hidden inside cells as well as by free virus. Mucosal transmission unusual for vaccine preventable diseases (Girard et al., 2004)	Yes Airborne (Smith, 2003)	Yes, complex vector borne (Vernick & Waters, 2004)
Dangerous and potentially fatal	Yes (Racaniello, 2006)	Yes, Indirectly by disabling immune system (Hilleman, 1995)	Yes (Smith, 2003)	Yes (Schofield & Grau, 2005)
Presence of suitable animal models and techniques	No/Yes. GM models now available (Ren et al., 1990), previously weak.	Yes/No Chimpanzees can be infected by HIV, but do not progress readily to AIDS. Monkeys progress to AIDS when infected with SIV (simian and therefore different version of HIV). (Feinberg & Moore, 2002)	Weak models (Griffin et al., 1995)	Weak models (de Souza & Ridley, 2002)
Natural Sterilising Immunity: Does the immune system ever completely clear the virus? Is spontaneous recovery normal?	Yes Genetic integration is not part of virus life cycle (Ohka & Nomoto, 2001)	No Obligatory integration of virus into host cell genome where latent infection may be immunologically undetectable (Zinkernagel, 2002)	No Estimated to be latent in one third of world population (Bentrop & Russell 2001)	No Obligatory integration into host cell genome where the infection may be immunologically undetectable (Rasti et al., 2004)
Genetic variation in virus type	Limited (Weiss, 2003)	Extreme (Garber et al., 2004)	High (Bentrop & Russell, 2001)	Very high (Ridley, 2002)

intellectual property protection may make co-ordination more difficult. Unsurprisingly, PPPs tend to be better at co-ordinating the later stages of vaccine innovation than early stage knowledge accumulation (Chataway et al., 2010). Whether strengthening intellectual property regimes – which influence the costs and trade-offs involved in co-ordination – constrains or encourages innovation is currently the subject of substantial debate. Future research might usefully explore how these changes influence the problems of knowledge accumulation highlighted in this paper.

In conclusion, the limited production of new vaccines does not necessarily indicate a lack of social concern, demand or funding. It also reflects a difference in difficulty of such a degree that some therapeutics and prophylactics may be beyond easy reach. Calls for more funding are likely to find backing from the analysis of this paper, but that backing is nuanced. Simply funding science without any governance in these situations may not generate solutions. Similarly, demand-side measures like competitions, prizes and purchase commitments, may not be successful if they are based on an assumption that the co-ordination of translational research is straightforward.

There are clearly trade-offs with the governance of research. Under conditions of uncertainty, decentralised exploration of multiple avenues has advantages in terms of search, but disadvantages in terms of co-ordination. Even with the benefit of hindsight, it is not clear which patterns of governance would be most appropriate for improving the co-ordination of translational research. Our current theoretical understanding focuses on the two extremes of decentralised markets and top-down, centralised control, but the implications of this paper suggest more attention is needed between these extremes to understand how the difficulty of seemingly intractable problems can be reduced by human agency.

Acknowledgements

This research was funded under the ESRC STEPS Centre Grant RES-588-28-5001, and the ESRC-TSB-NESTA-BIS IRC research grant RES-598-25-0054. The authors acknowledge Richard Nelson and Davide Consoli who helped with ideas and commented on earlier drafts. All errors remain the responsibility of the authors.

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