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Vaccine innovation, research translation and knowledge management: Testing processes in three polio trajectories

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Vaccine innovation, research translation and knowledge management: Testing processes in three polio trajectories

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Abstract:

How is clinical vaccine development managed? And what are the needed institutions for research translation and vaccine innovation? This paper identifies key features of knowledge accumulation by mapping out three technological trajectories of product development in the case of poliomyelitis. It highlights the importance of institutions that integrate knowledge and co-ordinate skills in testing processes, and emphasises the development of institutional capabilities in allocating testing resources, managing testability constraints, sharing knowledge and improving commensurability between testing communities. They are shown to play key roles in determining the rate and direction of innovation and innovation systems. Such features of knowledge accumulation can be missed in approaches that focus only on socio-political negotiations and narrow technology assessments that rely on static economic models of use and regulation.

1 Vaccine innovation and research translation: What are the needed institutions?

Pharmaceuticals are difficult and expensive to develop because there is a high attrition rate in drug development (Pisano 1997; 2006; Hopkins, Martin et al. 2007). But attrition is highest in the earlier stages of development, and less so in the clinical phases. As vaccines are moved out of the laboratory and into clinical trials, their development costs rise dramatically (Douglas 2004; Plotkin 2005; NIH and NIAID 2007). Why?

This paper explores the question by mapping out trajectories of innovation (Dosi 1982), where knowledge accumulates in specific technical and institutional conditions leading to the clinical development of poliomyelitis vaccines. It argues that clinical trials are not simply tests to verify safety; rather they are part of a more complex learning process that is required for pharmaceutical innovations to remain effective outside of the laboratory. In these latter stages of development, the process is more management intensive, as conditions become more difficult to control, and the process requires continual consideration for the appropriateness of the product being developed, relative to its desired market.

Product development can proceed along a number of long and costly paths before a product's behaviour in actual practice and its overall performance characteristics become clear. This in turn can make selecting between alternative courses of action difficult, the costs of which are, as Rosenberg identified, 'what economic analysis is all about'. The pricing of potential alternatives in the markets are often subject to large underestimates, and the costs of achieving greater clarity about alternatives are very significant indeed: 'Of particular importance is the fact that the great bulk of total R&D spending is for Development activities, not for Basic or Applied Research. Development expenditures accounted for approximately 67% of total R&D spending. These figures, at the very least, suggest great skepticism about the view that the state of scientific knowledge at any time illuminates a wide range of alternative techniques from which the firm may make cost-less, off-the-shelf selections' (Rosenberg 1994:13).

If science does not lead to a clear and costless path to technology, and markets for potential technologies suffer from a tendency to overlook this facet of innovation, there is a need to

understand what else is needed, and what activities are going on in development. This paper refers to these activities as the accumulation of technological knowledge and asks how it enables various technologies to emerge. It finds that co-evolving institutions have an important role to play (Nelson 2008b). The findings are relevant to policy concerns referring to 'research translation' and 'translational gaps (Cooksey 2006).

Building on a broader literature concerning the accumulation of technological knowledge (Layton 1974; Constant 1980; Vincenti 1990), the paper adds to work indicating that the rate and direction of vaccine innovation is influenced by the ability to set up 'testing regimes' and test repeatedly (Nelson 2008a; Yaqub 2008). Because theory is a weak guide to practice, the paper claims that there is an identifiable process underlying vaccine innovation: technologists test ideas with instruments and skill under varying conditions, according to shared standards, and with the active participation of co-ordinating institutions. This triad of elements (testing conditions, skills and instruments, and policy institutions) allows us to frame historical experiences in vaccine development as a learning process centred on the accumulation of technological knowledge. Testing regimes contribute to evolving capabilities across multiple institutions – a system of innovation (Lundvall 1992) - that includes the development of routines, methods, know-how (as opposed to only know-what), highly specific practices and procedures, experience of what tends to work and what does not (Nelson and Winter 1982; Pavitt 1999).

The accumulation of skills, co-evolution of capabilities and growth of shared knowledge across institutions over time is well described as a technological trajectory (Dosi 1982; von Tunzelmann, Malerba et al. 2008). [1] A key assumption of this paper is that there may be multiple pathways of clinical vaccine development in which testing is continually negotiated but not constructed.[2]

[1] '[Technological trajectories] resemble a world *a la* Feyerabend with different competing technological paradigms: competition does not only occur between the 'new' technology and the 'old' one which it tends to substitute but also among alternative 'new' technological approaches' (Dosi 1982:155). Dosi (1982:159) is careful to emphasise, that making direct analytical comparisons between paradigms and possible worlds is impossible to do *ex ante* and extremely difficult to do *ex post*. Kuhn (2000b) explains that this is because in order to understand some past (or future) body of knowledge, one must acquire an older (or non-existent) lexicon that is systematically different from the one used by the analyst. Statements contained within the body of knowledge under scrutiny cannot be accurately rendered, even if attempts are made to add to or translate current lexicons. This means that a technology evaluation or forecast undertaken at a single point in time has inherent limits to the degree of understanding and comparability that can be achieved.

[2] In these trajectories of development, testing is not 'socially constructed' because certain pathogenic features, along with highly rigid ethical and safety stances, affect learning processes in a way that are not open to alteration by human agency at social group or individual levels (Vincenti 1995). However, testing is negotiated by a diverse body of groups, and governance is required to appreciate and act on these

Technological practice draws on science in specific and limited ways that centre on the creation of testing conditions. Instrumentalities (Price 1984a, 1984b) – interpreted in this paper as physical devices, equipment and instruments, together with the skills to use them - can be of benefit to learning processes that have two opposing 'directions of fit' (Nightingale 2004:1260). In learning for science, instrumentalities help to control conditions which are not often repeated or replicated[3] but need to be highly simplified for identifying causal explanations (Hacking 1983; Deutsch 1997). In learning for technology, instrumentalities help to control conditions, where causal explanations are less important[4], but identifying reliable patterns and ways of replicating them in more complex environments becomes the name of the game. Such perspectives can be applied to medical innovation, where clinical knowledge is argued to be significantly independent from advances in scientific understanding; this has been referred to as an important 'point of discontinuity with the traditional literature on health technology diffusion' (Consoli and Ramlogan 2012). Thus, this paper builds on a growing body of literature concerned with the evolution of medical knowledge itself (Gelijns and Rosenberg 1994; Mokyr 1998; Metcalfe 2002; Nelson 2003; Metcalfe, James et al. 2005; Mina, Ramlogan et al. 2007).

Forward looking perspectives are required for pathways of innovation to be set out by technical and practitioner communities, as well as broader communities (Constant 1984; Brown and Duguid 1991). This is because technologies have a purpose that is not inherent to their physical properties (Polanyi 1958:328). Their purpose is derived from a broader collective set of competing 'social visions' that a designer can recognise either explicitly through interactions within their social communities (Constant 1984; Brown and Duguid 1991) or implicitly through tacit background knowledge accumulated through their experiences (Nightingale 1997). Purpose and function combine to form operational principles (how a technology works) (Vincenti 1990:209), and a shared vision is formed around which vaccine development efforts can accelerate, often in plurality (Blume 1992; Yaqub 2008).[5]

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differences alongside learning processes. Where skills and knowledge are distributed, governance is required to co-ordinate capabilities and resources for testing.

[3] Scientists rarely replicate or repeat experiments, they more often seek to improve and set precedents (Hull 1988).

[4] 'Technology can exist as an autonomous body of knowledge because it is *possible to know how to produce effects without knowing how those effects are produced*' (Nightingale 2004:1271, original emphasis).

[5] A more explicit insight into how social visions interact with technological developments can be found in the relationship between diagnosis (Rosenberg 2002), diagnostic instruments and the establishment of disease causation (pathology) (see Yaqub 2008). Before vaccine development efforts can take flight, there

However, development processes also involve learning and feedback, particularly from tests that are seen to be failures. So whilst biomarkers and correlates of immunity may establish technical standards that help guide the direction of trajectories (Eichler, Pignatti et al. 2008:819), they must also be capable of allowing developers to turn subjective qualitative desires into objective quantitative specifications and goals that can be tested for in progressively less controlled conditions (Vincenti 1988; Nightingale 2004). This is an expensive endeavour because theory and codified information is often a poor predictor of which behaviours are reliable and favourable for technological practice (Pavitt 1999). Development processes rely heavily on experimental interventions to produce empirical regularities (Hacking 1983; Yaqub and Nightingale 2012) that are useful.

Variations in experimental practice and instruments can mean that comparison is not possible; conditions or standards between tests may be different, accuracy and relevance may be checked with different instruments.[6] With low comparability, the interpretation of testing data in order to eliminate less suitable trajectories becomes subject to intense social negotiation as interests form around particular trajectories.[7] Governance structures can either co-ordinate various activities and instruments to increase comparability across conditions or it can provide leadership that mediates arguments about how the instruments are calibrated and the criteria for success or failure.

Co-ordination between research and development groups is needed to ensure that the new knowledge arising from testing processes is accumulated. This may involve the development of knowledge indexes or taxonomies where, for example, disease symptoms can be categorised or immune responses can be ranked. This allows for agreement and shared judgement to form over technical feasibility in learning and testing processes. Such 'invisible infrastructure' and 'testing regimes' (Nightingale 2004; Yaqub 2009) have important public good characteristics for the activity of multiple research groups and do not develop autonomously alongside technological

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are some critical elements – namely, a disease and an associated pathogen, and a diagnosis capable of characterising both reliably.

[6] Instruments can also be calibrated or designed to provide a way for standardisation. For example, rulers can be designed and distributed to allow distance to be measured in centimetres and not inches. Similarly, time can be measured by radioactive half life, but the watch is a more practical way of providing measurements in minutes and hours. In some cases of technological development, the range of instruments available for use may be wide, the scope for manipulating conditions large and the number of possible intermediate conditions high. In these circumstances governance becomes even more important.

[7] Parallel trajectories of development need not be completely commensurable in a strict translatable sense (Kuhn 2000a:37) because tacit background knowledge can be used by testing communities to interpret and infer which technical functions are not fulfilling their intended social purpose sufficiently well enough.

opportunities. They are a shared utility, created at high fixed cost, and need governance to set up and maintain.

The capabilities of private firms are widely acknowledged as being critical for medical innovation, even in neglected disease markets, but what role is there for non-private actors, and what might an 'entrepreneurial state'[8] look like in the vaccine system? Policies might be put in place to encourage the development of techniques and skills, and instruments and analytical tools so that test results feed back quickly. Efforts might be directed towards reducing the costs of supplying prototypes and models so that testing can be high volume. Attention to commensurability of testing processes could be made explicit so that knowledge growth is shared. These are overt governance challenges and attention to the evolution of such supporting infrastructure can be easily overlooked if research translation or a particular innovation is being zealously pursued.

2 Mapping technological trajectories in polio vaccine development

This paper provides an empirical exploration of policies relating to the accumulation of technological knowledge, and how these affected the innovation or (non-innovation) trajectories for a range of poliomyelitis vaccines.

2.1 Context for clinical polio vaccine development

When Landsteiner and Popper showed poliomyelitis was spread by an infectious agent in 1908, the development of a social vision for a vaccine was set in motion (Yaqub and Nightingale 2012). President Roosevelt and others concerned about poliomyelitis supported a vision that led to the emergence of a testing regime for the development of a vaccine. By 1947, after fatal testing failures in the 1930s, the testing regime had developed with intermediate conditions provided by a plentiful and steady supply of monkeys, new instrumentalities such as tissue culturing techniques that tightened feedback loops for experimental learning, and strong research institutions capable of co-ordinating large poliovirus typing studies (Yaqub and Nightingale 2012). Moreover, in 1953, poliomyelitis remained prominent and afflicted more than 20 per 100,000 in the United States (Robbins 2004:17).

[8] The author acknowledges Marianna Mazzucato using this term in personal communication 2010. See also http://www.demos.co.uk/files/Entrepreneurial_State_-_web.pdf?1310116014

During the 1950's, emphasis shifted from establishing operational principles (Polanyi 1958:328; Vincenti 1990:209) of immunisation in monkeys, to creating learning conditions in humans and the transition to clinical vaccine development. With a strengthened testing regime, the technical community was well prepared to appreciate any new ideas and vaccine developers were well positioned to start thinking about how they might test and assess ideas in people.

Clinical conditions would be more relevant and realistic than tests involving caged monkeys in laboratories, but the increased number of variables would make learning more difficult. For example, monkeys only contracted poliomyelitis if the agent was injected directly into their central nervous systems (Paul 1971:98), but testing on humans involved greater uncertainty about previous exposure to poliovirus. Institutions, such as the National Foundation for Infantile Paralysis, were needed to ensure that tests on humans would result in cumulative and reliable knowledge growth. Testing for a new technology required the co-ordination of skills and resources, and the development of new testing techniques.

With the chances of making a poliomyelitis vaccine much improved, a number of groups worked towards that goal but with different technological trajectories. Hammon chose to pursue a passive immunisation approach, whilst Salk and Sabin successfully pursued active immunisation approaches.[9] Salk took the line of a formalin-inactivated vaccine, whilst Sabin chose to pursue a live attenuated vaccine. The difficulties each of them faced are well documented (Carter 1965; Smith 1990).

2.2 Passive immunisation: Testing for design and field-based capabilities

A critical part of the vaccine design process can be described as a difficult and uncertain transformation of qualitative goals into objective ones. I begin by outlining the feasibility of passive immunisation as an operational principle, before analysing considerations made about vaccine design and organisational capabilities during the move to human testing.

[9] Passive immunisation refers to injection of blood gamma globulins that transfer specific antibodies to the virus, in contrast to active immunisation, in which an antigenic substance is injected that induces specific antibodies to the virus.

Hammon believed that gamma globulin, an antibody obtained from pooled plasma with known neutralising activity in the laboratory, might offer benefits in practice. Rather than prevent poliovirus infection, his immediate goal was to prevent infection causing disease on the nervous system (Carter 1965; Paul 1971; Plotkin and Vidor 2004). Permanent immunity through repeated infection might be achieved, but without the symptoms of poliomyelitis. The idea carried weight in part because passive administration of serum achieved some success against measles virus (MRC 1948).

In 1948 Morgan and Bodian were able to protect monkeys from one type of poliomyelitis (Carter 1965:64; Paul 1971:405). By using graded doses of virus with the purpose of producing varying levels of antibody, they effectively constructed an index of the degree of immunity in monkeys. This represented an improvement in the knowledge infrastructure because future antibody experiments conducted by different research groups could be compared to a shared index. Hammon argued that the role of antibody was still uncertain in humans, and that the antibody index would allow a safe start to ascertaining 'how much was enough for humans?' and 'how long do they last in the blood?'.

The Foundation created a 'Committee on Immunization' to manage strategic and logistic aspects of human vaccine trials (Carter 1965:125; Paul 1971:407). It was a daring role given the traumatic failures of the Brodie-Kolmer trials two decades earlier. Fear about using killed or live virus was a common theme voiced by Sabin and coloured the views of most in the field (Rinaldo 2005). However, Hammon's vaccine did not contain any virus and answered Rivers' call for boldness, "I think it is time that we got ready to go somewhere, and somebody ought to come up with some concrete experiments that will be done in human beings on a small scale in order to get going" (Carter 1965:126).

Hammon's preliminary field trial showed that relatively low levels of antibody could prevent invasion of the central nervous system (Hammon, Corriel et al. 1953). The results provided vaccine developers pursuing different trajectories, such as Salk and Sabin, not only with the confidence that disease could be prevented, but also a tangible performance criterion. The

subjective aim of immunity had become an objective goal of putting antibodies in the blood.[10] The testing regime had a bar, against which potential designs could be compared.

Questions of how quickly and safely immunity could be established in the blood, and how long it would last for in the blood under various conditions remained. Antibodies produced by the body through active stimulation were thought to last longer than those passively given to the body. Hammon argued the other non-passive trajectories had safety concerns and needed multiple injections, saying that with his gamma globulin, 'its effect would be immediate and would represent no danger to any child' (Hammon 1950:702). Although passive immunisation might not need multiple injections, Hammon apparently overlooked the fact that his subsequent clinical trial would seriously deplete all reserves of gamma globulin.[11] A further trial with more people, and hence more slightly varied conditions, was needed to address these issues of speed, durability and quality of immunity.[12]

The Foundation funded Hortsmann (1952) and Bodian (1952) to see if passive immunisation protected monkeys from very high, lethal doses of poliovirus of all three strains. Compared to Morgan's experiment in 1948, these conditions were more technologically relevant (because they involved all three strains), and perhaps even scientifically less interesting (because the theoretical concept of neutralising antibodies had already been established). The protection achieved under these conditions convinced the panel to fund a pilot study of 5000 children. Panel members realised that this size would not yield statistically significant results, rather the study's purpose was 'to gain experience in organisation and administration, as well as to evaluate the public's and medical profession's reaction to such a trial' (Rinaldo 2005:793).

[10] By helping to ascertain how much antibody was needed to prevent infection, Hammon effectively provided what can be called a correlate of immunity. Many HIV vaccine researchers lament on the lack of correlates of immunity (see for example Garber, Silvestri et al. 2004:398).

[11] The limited availability of gamma globulin restricted its use. Obtaining gamma globulin was an expensive and time consuming process and depended on voluntary blood donations. At the same time, the Korean War and hospital needs were drawing on supplies. O'Connor warned that there was not enough to provide 'even temporary protection to the 46 million children and adolescents most susceptible to poliomyelitis' (Rinaldo 2005:795). Nevertheless, the Foundation spent $7m boosting gamma globulin production and a further million children were protected in the poliovirus season of 1953 (Rinaldo 2005).

[12] The Immunization Committee initially turned down Hammon's request for a larger scale controlled trial (Rinaldo 2005). They wanted to see more animal and human data before embarking on a complicated and expensive clinical trial (the trial ultimately cost the Foundation $1m). They were also concerned about using placebo controls, which had never been used before, and its moral and social acceptability (Rinaldo 2005).

The details of the trial which needed to be organised were very broad.[13] Most critical was 'the definition of the severity of the paralytic disease, for which they used a carefully graded scale of muscle function loss' (Rinaldo 2005:793). Similar to the virus typing project, and the antibody index, this is another example where the Foundation set up an infrastructure to compare future observations to a set of known conditions, thereby ensuring that those observations would contribute to the cumulative growth of technological knowledge. It might otherwise have been seen as a chore, with little, if any, scientific merit.

The pilot results were encouraging and public support was very strong, with hundreds of volunteers being turned away by day four (Hammon, Corriel et al. 1953). Problems included such issues as lack of access to large autoclaves to sterilise the syringes and needles. A larger trial was quickly approved, which involved 55,000 children. The result of this trial was considered, 'conclusive evidence of a very significant reduction in the total number of cases of paralytic poliomyelitis' (Hammon, Corriel et al. 1953:758).

Hammon concluded that, 'perhaps the greatest contribution of the gamma globulin trials… demonstrated that a very low concentration of antibodies will protect man' (Hammon, Corriel et al. 1953:1283). Aside from taking this design standard from monkeys and establishing it in human conditions, a graded scale of paralytic disease was also developed. The trials were seized as an opportunity for the Foundation to build up organisational capabilities in acquiring local knowledge for testing outside laboratory conditions, and co-ordinating people, resources, logistics and public support. Alongside the accumulation of technological knowledge, the Foundation had begun setting up the organisational decision-making process for moving potentially more dangerous vaccines to trial in humans.

2.3 Killed vaccines: Testing regimes for taking 'calculated risk'

This section discusses how a more risky vaccine was tested in humans. The vaccine was more risky than Hammon's because it contained killed virus, but less risky than using live vaccine. The initial risk appears to have been borne by certain sections of society, who provided the conditions

[13] They included how to: blind the vaccine vials, select a type of control inoculum, source and set dosage of gamma globulin, types of syringes, packaging, venue, injection administration site on the body, consider legal aspects such as written informed consent, select geographical areas undergoing epidemics of a suitable magnitude, gain approval by local population, manage publicity and preparation of clinics, and follow up studies to identify incidence cases.

that were both relevant for technological development and suitable for learning. The resulting knowledge growth was shared and cumulative, as institutions put in place mechanisms to mediate differences in opinion, and co-ordinated carefully designed testing processes to manage the leaps from laboratory to animal and human settings.

By 1953, Salk had shown that poliovirus could be inactivated by formaldehyde (Salk 1953). Moreover, he determined how much formalin affected inactivation, and conducted safety and immungenicity studies in animals (Benison 1967; Robbins 2004). If there was any doubt as to whether such animal findings could be transferred to children, Howe's (1952) paper made it clear, entitled 'Antibody response of chimpanzees and human beings to formalin inactivated trivalent poliomyelitis vaccine'.[14] Salk, too, had started preliminary studies in humans which showed that antibodies could be increased to relatively high titres in children already infected at the Watson Home for Crippled Children.[15] But these advances, aside from any modern day ethical testing concerns, were leading to a somewhat problematic vaccine.

Conventional wisdom held that only a live-attenuated vaccine could confer long lasting immunity because it more closely mimicked a true infection (Carter 1965; Klein 1976; Smith 1990). Several of the Committee's senior virologists, such as Albert Sabin and the Nobel Laureate John Enders, questioned the relevance of antibodies and doubted the safety of a vaccine prepared from virulent poliovirus, regardless of how thoroughly it was inactivated, especially after the failed vaccines of the 1930s (ibid).[16] Enders is even quoted as having confronted Salk and calling his work, "quackery" (Carter 1965:88). But for Salk, the notion that only natural infection or a vaccine made of living pathogen could offer durable protection was nonsense (Carter 1965; Klein 1976; Smith 1990).[17]

[14] Howe tested six children at the Rosewood school, whom he noted as, 'low-grade idiots or imbeciles' (1952:265), and was able to report that 'both children and chimpanzees develop readily demonstrable neutralising antibodies at comparable levels following the injection of small quantities of clarified monkey cord suspensions containing formalin inactivated poliomyelitis virus' (1952:265).

[15] Like Howe, Salk tested children who were not infected but were 'mentally retarded' and found that the levels of antibody production were equally encouraging (Chase 1982).

[16] Enders cautioned, 'the ideal immunising agent against any virus infection should consist of a living agent exhibiting a degree of virulence so low that it may be inoculated without risk' (Enders 1954:88). Sabin persistently objected that a massive investment of time, money and public faith in a [killed] vaccine of only temporary use would hurt efforts to find a live virus that would really solve the problem (Smith 1990). Flexner declared that 'only an infectious vaccine compounded of living virus could protect' (Carter 1965:86).

[17] It is likely that Salk's deviation from the orthodoxy resulted from his newness to the field of poliomyelitis prophylaxis. In fact, his previous experience in developing inactivated influenza vaccine most probably directed his choice of approach to the poliomyelitis problem (Galambos and Sewell 1995:47).

Members of the Foundation acknowledged 'sharp differences' in the Immunization Committee and tried to manage them (Paul 1971:407). For example, regarding concerns about whether an inactivated poliomyelitis vaccine really was inactivated, Rivers said at a Committee meeting, "I think we will all admit that there is no *test* to be sure the stuff is inactive. Why not just accept that? Why kid ourselves? Why use the word inactive? Why not just say, 'safe for *use*?' It won't produce disease, and that's all there is to it" (Carter 1965:126, my italics).

Such 'nervous brawling' stalled any kind of progress (Carter 1965:129). So, in 1953, the Foundation set up a new and smaller committee because, as Weaver is quoted as saying, "The immunization committee was not able to function with the necessary dispatch. It could get entangled for months in technical debates. Furthermore, its members were virologists and the decisions on which we needed help were not exclusively virological. The Vaccine Advisory Committee with experienced public health men… was a far more efficient group" (Carter 1965:176; Paul 1971:411). The need for a second committee suggests that the design of tests is not an entirely objective and technical matter, and includes broader considerations. It was also established in part to limit conflicts of interest that may arise from having competing designers playing the role of "architect, carpenter and building inspector" all at once (Weaver quoted in Carter 1965:179).

Salk recalls the arbitrary nature of deciding when and precisely what to test. "All we had were several dozen experimental preparations, some with adjuvant, some without, some containing one type of virus, some another or a third or all three, some made with monkey tissue, some with testes, some inactivated for ten days, some for thirteen, some for twenty one" (Carter 1965:130). Salk insisted, "I don't know that we even have a vaccine yet. That term was used, but I think it should be understood that we are using it as a colloquial expression. We have preparations which have induced antibody formation in human subjects" (Carter 1965:152). The possible permutations of experimental conditions Salk describes seem endless. Moving to major field trials involved uncertain but skilled judgement about what effects were likely to be reliable, and Salk was pushed into readiness by the Foundation.

Brodie and Kolmer had tarnished the killed approach and Salk was careful in his relations with the public to set apart his methods from theirs; for example, a Time magazine article pointed out, in unusual technical detail, that Salk's vaccine used purified mineral oils to hold the vaccine in the body for longer as a way of distinguishing his from previous efforts (Time 1953).

Salk's uncertain vaccine was moved into trials with a sense of purpose and social conscience.[18] Rivers asked, "Wouldn't it be silly to wait 50 years or to wait 10 years to develop the ideal vaccine when there is the possibility of a vaccine being developed very rapidly that will last, say, for two or three years with one injection perhaps? We don't know anything about that, but have we the right to wait until the ideal vaccine comes along?" (Carter 1965:151). Although Rivers thought the Salk vaccine was 'something slightly better than gamma globulin, something by definition imperfectible,' he felt it was 'worth a try' (Carter 1965:152). From these exchanges, it seems that vaccine development is not a process of optimisation. Vaccines are developed to function only sufficiently well enough to fulfil a social purpose. That purpose drove the Foundation to begin planning for a major field trial.

Harry Weaver wrote, 'The practice of medicine is based on a calculated risk…the physician elects to follow the course that provides the greatest benefit with the least risk of incurring any untoward effects… If [we wait until more] research is carried out, large numbers of human beings will develop poliomyelitis who might have been prevented from doing so… our work must be governed by scientific and sociological concerns' (Carter 1965:147; Benison 1967).[19] The vaccine development process was not simply a scientific puzzle, with a technical solution that could be found and optimised; rather, the urgency of the historical and social context of the actors played important roles in their decisions about an 'imperfectable' vaccine.

In the design of the trial, the planned use of placebo controls was problematic, but the precedent seemed necessary. Initially, Weaver sought simplicity and economy, and suggested that the poliomyelitis rate be compared between vaccinated and non-vaccinated school-children of the same age (Carter 1965:176). However, the Vaccine Advisory Committee suggested that socioeconomic differences between those who volunteered and those who did not would weaken the study.[20]

[18] A member of the Vaccine Advisory Committee said, "I think… progress can be made even in the light of the fact we have so little knowledge. It would seem to me the time has come to really go at the inactivated material… The live virus is fine, but if you think about it as a public health measure, it is a difficult thing to use… I don't think you have a good excuse morally to go into infectious material until we have shown that inactivated material was unsatisfactory" (Carter 1965:128).

[19] The trade-off was emphasised in a telegram to convince sceptics, 'It is said that to await certainty is to await eternity' (Smith 1990:295).

[20] High income, well educated families were more likely to submit their children to experimentation of this kind. In contrast, less well educated families living in poorer areas were less susceptible to paralytic poliomyelitis, tending to contract the non-paralytic form in infancy and gaining immunity. Such a project would only immunize the children most susceptible. The poliomyelitis rate in the vaccinated group might be similar to that among the unvaccinated. Therefore the vaccine might be good, but the test would not

Salk felt that his vaccine was not up to such a stringent test, and lapses in the manufacturing process or unimpressive results of a double-blind test might scupper the opportunity to improve it (Carter 1965:178). I quote him at length in the paragraphs below to show that the design of the tests was at the centre of his concerns at the time, and that the parameters of the tests left an indelible mark on the nature and characteristics of the vaccine.

> "The sensible thing, I thought, was to accept the urgencies of the situation and continue improving the vaccine. I thought the field trial should be designed to permit this, not prevent it… I thought we should concentrate on polio prevention and be less concerned about making epidemiological history with an elegant double-blind study. I was afraid that, for some people, the *kind* of test had become more important than the kind of protection the vaccine might be able to provide."

> "I wanted to know who had been vaccinated so that blood samples could be taken promptly. If tests then showed that a certain batch of vaccine was producing unsatisfactory results, the children could be revaccinated with better material. At the same time, we could be taking steps to improve the manufacturing process and avoid new batches of inferior vaccine. Finally I was uncomfortable about giving placebo shots to children, depriving them of immunity in what might turnout to be an epidemic year. Many public health officials agreed with me on this."

> "You had this rigid insistence that a 'product' be submitted forthwith for ceremonious testing. The emphasis on 'product' and on ritual and on looking good in the eyes of certain elements in the scientific community was being allowed to obscure the real purpose of everyone's work, which was the prevention of polio" (Carter 1965:178).[21]

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have the resolving power to prove its efficacy. In addition, poliomyelitis diagnosis was still difficult despite the scale developed in the Hammon trials, and any biases emerging from knowing who had been vaccinated and who had not, would serve to exacerbate the problem.

[21] Salk went on to describe the use of placebos as 'a fetish of orthodoxy… a beautiful epidemiologic experiment over which the epidemiologist could become quite ecstatic but would make the humanitarian shudder and would make Hippocrates turn over in his grave… the worship of science involves the sacrifice of humanitarian principles on the alter of rigid methodology' (Carter 1965:192).

In order to address the concerns of parents, teachers, and such 'humanitarians' O'Connor announced that an observed control plan would be used, in which children would not be injected but only observed (Meldrum 1998). The Foundation asked health officers for advice and support, who suggested that the Foundation may not be able to maintain impartiality in such evaluation (Meldrum 1998). So O'Connor appointed Thomas Francis to head the evaluation of the trials, a critical but unglamorous task, based on 'his deft direction of complex field trials of influenza virus vaccines during World War II' (Markel 2005:1408). However, Francis would not accept until he manoeuvred between health officers, paediatricians, clinical poliomyelitis specialists, statisticians and virologists to engineer a change in the trial design (Meldrum 1998). He suggested a placebo design run in some areas at the same time as an observed design run in other areas.

Addressing concerns about volunteer recruitment in the placebo plan, the evaluation group decided that it could rely on the widespread fear of the disease; members agreed that 'it would not be difficult to sell as there is a high attack rate… [and] there would still be a 50% chance of a child receiving the vaccine' (Meldrum 1998:1235). Francis compromised with Salk and others to a certain extent with observed design in some areas, but his insistence on the placebo plans in other areas was particularly important in the context of the vociferous criticisms from Enders, Sabin and others about the validity of the killed-vaccine concept.

Firstly, results emerging from double blind trials might be more convincing, and facilitate quicker and more widespread vaccine adoption. Secondly, it was important given the possible conflict of interest arising from the Foundation evaluating a vaccine they, as an organisation, developed and sponsored. Thirdly, the placebo plans were also a part of the Foundation's effort to legitimise an institution governed by non-experts.

The trial for the vaccine went ahead in 1954 and was the largest of its kind to be run. It was not a cheap gamble, grants for the field trial and its evaluation cost the Foundation a total of $7.5m. The results of nearly 2 million children were presented on 12th April 1955, and the vaccine was found to be safe and 70% effective (Smith 1990). Although not completely effective, the breakthrough cases[22] were judged to be less severe (Smith 1990). With financial guarantees from the Foundation, industrial production facilities were already built and ready to operate (Blume

[22] Cases where volunteers are diagnosed with poliomyelitis despite being vaccinated in the trial.

and Geesink 2000). The Foundation paid a further $7.5m to the manufacturers for 10 million Salk vaccine doses (Chase 1982). The products of six producers were licensed within days, one of whom was Cutter Laboratories in Berkeley (Offit 2005).[23] Poliomyelitis cases dropped from 58,000 in 1952 to 5,600 in 1957.

Paul, whose career in poliovirus research spanned both eras, contrasts the 1935 and 1955 vaccines. 'The situations were in no way comparable, for the Brodie-Kolmer vaccines had been launched in the face of colossal ignorance, whereas the Salk-type vaccine had been promoted under circumstances which from the start almost guaranteed success. And yet one cannot help feeling a twinge of sympathy for the two figures of 1935 who were so alone in the midst of their disgrace, in contrast to the powerful forces of the National Foundation, the US Public Health Service, and innumerable advisory committees that stood back of the Salk type vaccine' (1971:420). Paul notes how different the testing regimes were and how the difference critically changed the environment from which a vaccine could emerge.

2.4 Live vaccines: testing in the shadow of the killed vaccine

This section reviews how improvements to the testing regime enabled the establishment of live vaccine trajectory. It emphasises the historical-dependency of such trajectories by highlighting the role of non-fiscal testing resources, shows how dependent technological trajectories become on context, systems and testability constraints, and ultimately describes different decisions taken by public health authorities in the USSR and USA.

As he had done with the yellow fever virus, Max Theiler passaged the poliovirus continuously through the brains of living mice until, without losing its capacities to stimulate an immune response, the attenuated virus no longer caused paralysis (Chase 1982). He reported it to the Foundation in 1946, which then funded further research to see if poliovirus could also lose its

[23] The Cutter incident represented 'one of the worst pharmaceutical disasters in history' (Offit 2005:1411). In a batch of Salk vaccine manufactured by Cutter, there remained some virus which had not been killed. It caused over two hundred cases of poliomyelitis, of which 150 were paralytic and 11 were lethal (Nathanson and Langmuir 1963). The error paralysed 15 times more children than the earlier Brodie and Kolmer vaccines combined.

ability to infect the central nervous system – which it did on repeated passage through non-nervous system tissues (Robbins 2004).[24]

The live attenuated poliomyelitis vaccine approach was feasible only after certain developments in the testing regime because the approach relied on striking a balance between efficacy and safety. This entailed searching for virus that is not pathogenic (disease causing) but retains some of its virulence (ability to infect). By strengthening the testing regime, the Foundation enabled safe learning in humans (Yaqub and Nightingale 2012) through variation-selection (Campbell 1960; Vincenti 1994). The development of tissue culture techniques[25] facilitated the rapid emergence of variation in strains, whilst the availability of monkey models allowed vaccine developers to select for pathogenicity and virulence traits[26], and the typing project allowed putative vaccine preparations to be challenged without added confusion.

Sabin was one of several groups[27] working in this way (Paul 1971; Robbins 2004). In light of the improvements to the testing regime noted above, the Foundation provided him with $1.2m between 1953 and 1961, and $2m in total (Carter 1965:357; Chase 1982:303). In 1955, Sabin began a trial on inmates in Chillicothe Federal Prison in Ohio (Carter 1965:357; Smith 1990:301). His vaccine was successful, but the Foundation saw little reason to take chances with a larger scale trial of an infectious live vaccine when Salk's field trial had demonstrated efficacy the previous year. Large scale trials of Sabin's vaccine, and those of others, would be difficult to interpret because the Salk vaccine had been licensed and was being used widely. For example, when, in 1959, Herald Cox had the opportunity to test his live vaccine in Miami, Florida, Sabin dismissed any excitement by pointing out that too many people had taken Salk vaccine for the test

[24] The idea of attenuating the poliovirus, rather than killing it outright, appealed to many because it was presumed to mimic the natural situation more effectively, resulting in a longer and more effective immunity. However, Salk, and other proponents of killed vaccine, resisted the notion that immunity provided by live vaccine would be somehow longer lasting. 'One cannot say how long immunity may last, one can report only how long it has lasted' (Carter 1965:377).

[25] Viral culture techniques were significantly improved by Dulbecco and Vogt (1954). Adapting techniques for growing bacteria, they grew virus in microscopically thin mono-layers of chick embryo tissue cells. The colonies proliferating from the growth of a single viral particle could be identified, counted and isolated. This made it easier to purify specific lines of virus, which was extremely valuable for those looking to prepare a live vaccine (Paul 1971:406; Robbins 2004:19).

[26] Selecting strains with monkeys meant that live vaccine development did not need to rely on few and imprecise in-vitro markers of virulence, such as growth at higher temperature (Paul 1971:458). Instead, a more authoritative test for neurovirulence, adopted as the standard by the regulatory agencies, was devised where monkeys had to be inoculated through their central nervous system (Robbins 2004:20).

[27] Other groups were led by Hilary Koprowski at the Wistar Institute, Herald Cox at Lederle Laboratories, and Joseph Melnick at Yale, all of whom tested their prototype live vaccines on institutionalised children (Chase 1982).

to mean anything (Carter 1965:365).

There is clearly a strong path-dependency element to testing processes in vaccines (see also Blume 2005), but I would like to draw attention to a slightly different view. In the early experiments, poliomyelitis researchers faced a shortage of virus; Evans and Green, who were beaten to the Nobel Prize, faced shortage of human embryonic tissue; Hammon faced issues with a shortage of gamma globulin; whilst Sabin faced a shortage of people to test on. These cases represent a scarcity of testing resources. These resources are not fiscal, as is commonly emphasised in health and vaccine development literature (see for example, Lanjouw 2003; Archibugi and Bizzarri 2004; Arnold 2005; Barder 2005), but can be anything from the availability of monkeys, gamma globulin, primary isolates, to simply people as test subjects. They were unlikely to have been resolved by market failure approaches or policies that focussed on pecuniary issues alone.

The safety concerns in this trajectory extended beyond simply whether the virus in the vaccine was sufficiently attenuated to prevent it from causing disease. The major concern centred on its genetic stability and whether the attenuated virus would *remain* safely attenuated. One of the advantages of the live vaccine was that after it passed through the intestines and was excreted by the vaccinee, it might then go on to confer immunity to someone else in the community. But the same advantage became a disadvantage for those who thought that, after several passages through the community, the altered vaccine strain might undergo progressive genetic changes such that it reaches a degree of virulence comparable to that of wild epidemic polioviruses. The success of the entire live approach therefore turned on proving that any cases of poliomyelitis was not caused by the vaccine reverting back to virulence after replication in the host.

Melnick found that live vaccine virus passaged through children was sometimes virulent enough to paralyze monkeys (Carter 1965:381). This caused serious concern, but there was no way in which a test could show that a given case of poliomyelitis in humans had been caused by the live vaccine, even if the victim was struck by poliomyelitis shortly after taking a live vaccine. If virus recovered from the victim resembled the wild type, one could suppose that it had taken over the intestines, and driven away the vaccine virus, before causing the disease (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 not be able to prove a vaccine guilty.

This made designing a test for measuring live vaccine safety virtually impossible, never mind one that could be compared to the safety of a killed vaccine. In the absence of a test that could offer commensurable assurances of safety, the live vaccine continued to be perceived as being more risky.[28] Closely tied with these perceptions were the assumptions of the vaccine designers, about the social context in which their designs would be used. Safety would become more readily observable as a systemic feature, as protagonists argued risks and benefits in different contexts.

Due to safety concerns and the prior use of Salk's vaccine, Sabin was forced to look abroad to conduct large scale trials. In 1958, 200,000 children in a Singapore trial received Sabin's live vaccine in an effort to curtail their epidemic (Paul 1971:454). By 1960, approximately 100 million people in the former USSR and Eastern European countries had received the vaccine. By the end of the year enough evidence had been established to secure licensure in the US for Sabin's live vaccine (Paul 1971:456).

However, the continued existence of distinct trajectories depended on variation in health systems because a given vaccine-attribute could serve as a merit in one and as a drawback in another. As a Soviet public health official remarked, "Our inoculation program was a public-health measure, not a field trial. It was designed to suit our medical services. In attempting to inoculate a population the size of ours, could there be any serious confusion about whether to give away candy drops, when the alternative was injection requiring so much more apparatus and personnel? Our work with the Sabin vaccine must be viewed in terms of public health and not as a strictly controlled scientific experiment" (Carter 1965:359).

If the Sabin vaccine could actually be shown to cause paralytic poliomyelitis, the finding would have been more significant for the US than for the Soviet Union. The Soviet Union was suffering poliomyelitis incidence rates of 94 per million (Carter 1965:363), much higher than that of the US, so any vaccine that could reduce that figure faster (because it could confer immunity to the

[28] Tommy Francis played down the difficulties of designing comparable safety tests. "The two outlooks are, then, simply, this. Inactive virus is apparently a test of the straightforward hypothesis that antibody induced by the administration of antigen can provide protection without subjecting the recipient to harmful effects of even apparent infection. The other, through the use of modified active virus, seeks to induce antibody formation but wishes to add some undesignated advantage derived from assumedly harmless infection (I am not certain that any significant infection may not create undesirable tissue reactions…). Which of these approaches to poliomyelitis will be the more effective is, then, not a decision to be arrived at by authority and debate but by… making the observations. When the conditions are appropriate, tests should be made." (Carter 1965:357).

non-vaccinated too) would be allowed the deficiency of a few vaccine-caused cases. It only represented one dimension in a broader set of criteria for the health system as a whole.

The protagonists of each vaccine promoted their interests and preferred choice, but the way in which a vaccine's attributes complemented existing infrastructure and health systems is likely to have had a greater influence in determining their adoption.[29] The ensuing history of the changing relative merits and drawbacks of the Salk and Sabin vaccines has been astutely discussed elsewhere (Blume and Geesink 2000; Blume and Lindner 2004; Blume 2005). It is worth noting, however, that as incidence of poliomyelitis decreased in the US over the next thirty years, the perception of risks and benefits changed and so the choice of vaccine changed too.[30]

2.5 The changing importance of thermostability in polio vaccines

The development of a more thermostable poliomyelitis vaccine was made a high priority in 1991 by the Children's Vaccine Initiative (CVI)[31] to benefit parts of the world where health systems cannot support cold chain refrigeration. This section shows that whilst a plausible operational principle was developed, the social vision and broader imperative to accumulate the necessary technological knowledge was weak. Notably, the theoretical notions highlighted above in a history of the Salk and Sabin vaccines can be used to frame more contemporary debates regarding certain attributes of vaccines appropriate for developing countries (Kristensen and Zaffran 2010), such as thermostability (Chen and Kristensen 2009).

[29] Cox was benefiting from an aggressive publicity campaign by Lederle touting its advantage of a single dose vaccine that still protected against all three strains (trivalent) (Carter 1965:365). Koprowski managed to trial his vaccine in 9 million people but had his vaccine turned down by the US government because it caused some lesions in monkeys (Paul 1971:454). Salk argued that his vaccine was effective and that they needed to wait longer, without introducing other vaccines, to see definitive results of an imperfect vaccination program. And Sabin's appeared to be the newer more modern vaccine with which the public health service could have a second chance of executing a vaccination program of more complete coverage (Carter 1965:372). Sabin's field trials in the Soviet Union were so effective they were doubted, and it took a report by Hortsmann, who was dispatched there by the WHO, to verify the standards and evidence (Paul 1971:455; Robbins 2004:20).

[30] 'The conclusion [of a comparative analysis of live and killed vaccine] is heavily dependent on assumptions of risk of exposure to wild virus in the US. Major declines in risk of exposure… could alter the balance significantly' (Hinman, Koplan et al. 1988:295). Despite the high costs of switching from live to killed vaccine, the Advisory Committee on Immunisation Practices recommended the change in 1996 and US vaccine policy delivered killed vaccine exclusively from 2000 onwards (Plotkin and Vidor 2004:1484).

[31] Muraskin (1998) provides a detailed account of the origins of the CVI and some of its activities, but focuses on the political difficulties the organisation faced.

The need for a thermostable vaccine emerged from the way the technological systems and infrastructure of immunisation evolved. A large proportion of the total cost and effort of immunisation programmes relate to the creation and maintenance of a cold chain to ensure that vaccines are kept in conditions where they can retain their potency until the point of final delivery (Levin, Levin et al. 2007).[32] The cold chain system had to be geared up to cope with the least stable vaccine; which in the early 1990s was Sabin's poliomyelitis vaccine (Lemon and Milstien 1994).

As the movement towards poliomyelitis eradication gathered momentum, thermostability of the vaccine became a more significant issue. By 1990, poliomyelitis cases had been reduced to a lower level through mass vaccination programmes - for example through national immunisation days at schools (WHO-EPI 1992; Hull, Ward et al. 1994). It was envisaged that this strategy could continue, but soon a 'mopping up' strategy would be needed that relied on: firstly, an effective surveillance network for monitoring the appearance of every possible poliomyelitis case, however remote it may be, and secondly, house-to-house administration of the vaccine to those at highest risk of poliomyelitis to interrupt transmission and eradicate the virus (Chen and Orenstein 1996; Aylward, Arnab et al. 2003).[33] Eliminating the last 5% of cases has proved to be difficult because they often extended beyond the reach of the cold chain network and infrastructure.[34]

To co-ordinate development efforts between a number of universities, vaccine institutes and commercial firms, a Product Development Group was established in the CVI (Lemon and Milstien 1994).[35] The mobility of immunisation workers was identified as critical for eradicating poliomyelitis. Workers' mobility could be sharply increased in those hardest-to-reach areas if a

[32] The costs include capital outlays on refrigeration equipment but also expenditure on maintenance such as, procuring adequate fuel, ensuring reliable power supply, undertaking repair and management of the systems, and educating users of the dangers of over-refrigeration and vaccine freezing. Freezing can occur if vaccines are placed too closely to the walls of ice-lined refrigerators, or embedded in ice-packs that have not been allowed to melt a little. Taken together, these issues represented 8% of the total costs of immunising a child in parts of the developing world (WHO-EPI 1992). Freeze sensitive vaccines constituted over 31% of the US$439 million that UNICEF spent on all vaccines in 2005, and more than three quarters of all vaccine shipments were exposed to freezing temperatures at some point during distribution to health centres (Matthias, Robertson et al. 2007).

[33] The projected need for a two step strategy of mass campaigns followed by specific and focussed projects turned out to be largely correct. Twelve years after the poliomyelitis eradication goal was set in 1988, cases declined by 95% worldwide (Hull and Aylward 2001).

[34] It was also challenging because skilled workers need to engage, persuade, and negotiate with each individual household's views about the vaccine and their localised knowledge systems (Leach and Fairhead 2007; Yahya 2007).

[35] This was sponsored by Canadian International Development Agency and Rotary International (Lemon and Milstien 1994).

thermostable vaccine could be developed, one that could be carried 'in the pockets' of workers for several days. Vaccine designers translated these qualitative attributes into quantitative goals, just as Hammon did when he demonstrated how much antibody was needed, just as Salk did when he showed how much inactivation was needed, and just as Sabin did when he showed how much attenuation was needed. The target was set to develop a vaccine that could withstand 37°C for 7 days, and retain a potency after such a thermal challenge of <0.5 $\log_{10}$ loss of titre of each of the 3 vaccine strains, with minimal change to viscosity (Milstien, Lemon et al. 1997).

There were a number constraints placed on vaccine developers. First, any changes to the vaccine must be capable of transfer to most poliomyelitis vaccine manufacturers. Second, no attempts should be made to alter the Sabin vaccine's thermostability through genetic manipulation because it would 'raise very complex safety issues that would substantially delay testing and introduction of a new vaccine' (Milstien, Lemon et al. 1997:248). These constraints show that any potential thermostable vaccine would have path dependent characteristics that depended on how the capabilities of vaccine producers around the world evolved, and on how Albert Sabin happened to settle on a particular set of poliovirus strains for his vaccine more than 40 years ago.

By 1995, a new operational principle of thermostability had been established. Wu et al. (1995) showed that suspension of poliovirus in 87% deuterium oxide (D_2O, known as heavy water) results in a significant increase in the stability of the virus when incubated at 37°C 42°C or 45°C. It was not understood exactly why stability is improved, there were some hypotheses put forward following the demonstration of this stabilisation effect (Newman, Tirrell et al. 1995), but what made this an operational principle is that the stabilisation effect was recognised as being strong, predictable and useful. There is a dramatic 295 fold increase in the stabilisation effect of $D_2O/MgCl_2$ as temperature increases to 45°C when compared to the $H_2O/MgCl_2$ stabilisation agent (Wu, Georgescu et al. 1995). This makes the behaviour of the vaccine within the broader social and technical system much more reliable.

But the operational principle of thermostability was not developed further and the trajectory was aborted. Concern over scarcity of vaccine resources played a role in hindering the development, just as it had done for that of the Sabin vaccine. There were controls on the movement of heavy water isotopes, which is an essential component in the preparation of nuclear weapons.[36]

[36] Controls could have been placed on the vaccine developer, but in view of the possible large number of doses involved and the relative ease with which 90% heavy water can be further purified, controls on the

Morever, it remained clear that developing a thermostable vaccine would not eliminate the need for cold chain systems because other essential vaccines would still need refrigeration. Improving the thermostability of a single vaccine would have had a negligible effect on reducing the overall cost of maintaining the cold chain infrastructure. This is likely to be at least as true today as it was then, and reveals the systemic path dependent nature of technological trajectories.

The development of vaccine vial monitors (VVM), and the associated training of health care workers in using them (Thakur, Swami et al. 2000), also inhibited the development of thermostable vaccines. VVMs can indicate the time and thermal inactivation for each individual vial, and can allow health centres to use remaining contents of a vial until it is completely empty (Zweig 2006). VVMs can help ensure quality and safety of vaccine delivery in weak infrastructure settings, but it can also help reduce wastage and increase efficiency in terms of number of doses actually delivered per vial (Guichard, Hymbaugh et al. ; Setia, Mainzer et al. 2002). Indeed VVMs are being used for evaluating how effective cold chains are, locating weak links and breaks in the cold chain, and identifying incidences of vaccine freezing (Samant, Lanjewar et al. 2007). So, VVMs are actually helping to strengthen the cold chain paradigm by monitoring the stability of heat-labile vaccines, thereby making the development of a thermostable vaccine a lesser priority.

There may be a view that vaccines, when developed, do not require continual development and change. If a vaccine is safe and effective, one might think there is little else left to consider in vaccine innovation. A market study funded by the Product Development Group found that public reaction to a new poliomyelitis vaccine was more favourable when the vaccine was presented using words such as ‘updated’, ‘long-lived’ and ‘preservative’ rather than ‘improved’, ‘thermostable’ and ‘isotope’ (Milstien, Lemon et al. 1997). Such reactions suggest that deeper (rather than simply broader) dialogues are needed if we are to avoid resorting to prescribing ‘cultural change’ as remedies to many of our technology adoption ills.

movement of the vaccine itself would be difficult to implement. Such challenges are similar to other ‘dual use technology’ problems, where suggested policy solutions centre on developing institutional capabilities which recognise there is little or nothing inherent in technologies’ physical components that dictates their purpose; guardianship and governance structures need to evolve norms that structure appropriate technology use (McLeish and Nightingale 2007).

With the position of the WHO-EPI that poliomyelitis could be eradicated using the existing vaccine, that a more thermostable vaccine would not help, indeed a heavy water preparation could hinder vaccination efforts, the Product Development Group recommended in 1996 that its work be terminated. The case illustrates how difficult it can be to update and continue multiple trajectories where the technology is systemic and the market is not clearly a lucrative one. For a new vaccine, for which disease burden is typically known, markets can be estimated. But for improving or modifying a vaccine, technological knowledge can be harder and more expensive to build up though clinical trials. Market research on the words with which to present potential new vaccines may help, but more critical is a set of public institutions which are capable of appreciating how vaccine technologies can and have evolved, often with considerable interdependence with other technologies, such as VVMs or cold chain systems.

3 Discussion

This paper has explored why the development of pharmaceutical products is so management intensive by offering a history of poliomyelitis vaccine development and drawing on the notion of technological trajectories of knowledge accumulation. It reiterates a call made nearly two decades ago to redress a 'curious neglect' of this process of knowledge accumulation through testing (Rosenberg 1994:14):

> 'The extent to which total R&D spending is dominated by the Development component calls attention to critical aspects of the manner in which technological knowledge grows. It is misleading to speak of some as-yet-untried but on-the-shelf technologies as 'known'. It is the essence of these technologies that their designs need undergo protracted periods of testing, redesign and modification, and retesting before their performance characteristics are well enough understood for them to be produced and sold in reasonable confidence. Although these expensive and time consuming development activities are typically not of great interest for their specific scientific content, the information so acquired is absolutely essential from an economic point of view. Performance characteristics of high-technology products simply cannot be accurately predicted without extensive testing… It cannot be emphasised enough that such information typically cannot be deduced from scientific principles… [Moreover], such

uncertainties are of very limited interest from the point of view of academic science' (Rosenberg 1994:14).

By 1950, some might have claimed that 'the science was more or less there'.[37] In contrast, this paper has shown that considerable further technological knowledge needed to be accumulated in clinical contexts (rather than in laboratories and monkeys) in order for effective vaccine products to emerge. Little about these efforts could be described as inevitable; they were focussed on identifying which clinical attributes were most important for humans, and this section summarises how these were built into vaccine products through testing processes. The barriers to vaccines were therefore not scientific but institutional in nature, and they were overcome by co-ordinated development efforts.

Developing a testing regime to accumulate technological knowledge involves co-ordinating institutions that help ensure qualitative attributes are interpreted into quantitative targets for the development of operational principles. This was shown in the paper in the thermostable vaccine as well as the Hammon, Salk and Sabin vaccines. Both the Foundation and the CVI focused on transforming subjective issues of vaccine design into more specifiable, objective criteria for vaccine use in human conditions (rather than in laboratory monkeys). The Hammon trials provided all vaccine developers with an important correlate for immunity, a quantitative design standard, by showing that relatively little antibody was needed for efficacy. Salk demonstrated how much inactivation was needed and Sabin showed how much attenuation was needed. With the thermostable vaccine, tangible targets were set not only for heat durability, but also for temporal durability, potency, and viscosity.

The Hammon trials also improved field-based capabilities for testing. The growth of knowledge emerging from these field trials was scaffolded to make knowledge accumulation (rather than fragmentation) more likely. This was achieved at significant fixed cost through careful standardised trial designs, establishing critical viral infection doses, and developing various

[37] Some might claim that 'the science' was in place even earlier after Flexner demonstrated that monkeys surviving poliomyelitis could resist re-infection in 1910. Indeed, Flexner claimed that a vaccine would be ready in six months. However, previous work by the author showed that significant technological knowledge concerning poliomyelitis vaccine development needed to be accumulated in a strengthened testing regime, that ran alongside further scientific investigations (Yaqub 2009). By 1950, poliomyelitis could be manipulated in test tubes, tissues, and monkeys, and was known to exist in three (and only three) virus types.

indices of immunity and diagnosis[38]. Together, they formed an important part of the invisible infrastructure against which field tests could be evaluated.

Through the Hammon trials, the Foundation strengthened its administrative capacity for coping with the logistics of large scale immunisation and co-ordinating the supply of testing resources. It co-ordinated with many different actors to ensure that the field testing of vaccines ran smoothly, and that any putative vaccine would fit within the broader technological system. Whilst this was not possible for the thermostable vaccine, Hammon's and Salk's clinical trials were greatly facilitated because the Foundation ensured officials from health departments across the country were on board. They provided local knowledge and support when the Foundation needed to navigate through the sensitive issue of using placebos in the trials for the first time.[39]

The Foundation retained at its core a social purpose whilst trying to create an environment that was conducive to technological research and development. It was important to ensure there would be volunteers to test on, gamma globulin to test with, and a public tolerant of failures (such as those by Brodie-Kolmer and Cutter Laboratories). The management of clinical trial participants made the introduction of double-blind, placebo-controls possible. Such protocols indicate a strong emphasis on testing for learning and knowledge accumulation rather than testing for simple validation and certification; it is an example of how well the Foundation juxtaposed public concerns with those of the scientists. The design and timing of clinical trials most likely had a lasting effect on the characteristics of the Salk vaccine when it was licensed.

The antagonism between the orthodoxy, of which Sabin and Enders were part, and newcomers such as Salk, might have mired all development efforts were it not for a mediating organisation[40].

[38] Firstly, an index was developed to gauge how much antibody was needed for immunity in monkeys. Secondly, the trials allowed a similar index to be constructed for humans, which addressed crucial questions about the longevity and efficacy of neutralising antibodies for human immunity. Thirdly, graded scales were developed to measure varying degrees of severity in the symptoms of poliomyelitis.

[39] In addition, the prevailing and very eugenically oriented medical ethics of the first half of the 20th century (see for example Martin 1998), which considered mentally and physically handicapped children and prisoners to be the subjects of choice for medical experimentation, had the effect of strengthening the testing regime by providing easy access to realistic testing models.

[40] The patterns of institutional rewards and credit accorded to Salk and Sabin differed significantly suggesting that the pursuit of elegant science and urgent technology development are distinct endeavours with opposing 'directions of fit' (Nightingale 2004). Salk was a household name but his colleagues in the science community never afforded him the recognition and awards accrued to Sabin (Oshinsky 2005:270). 'Many attributed the professional discrimination against Salk to the flamboyant backing of O'Connor and the resultant media frenzies, which were offensive to 'pure scientists'' (Katz 2004:187). Although Salk

The Foundation established mechanisms for mediating differences of opinion about efficacy, safety and when to test. One principal means for doing this was to strengthen the test by insisting on an unprecedented placebo arm, against the wishes of Salk who described it as a 'fetish of orthodoxy'. Another means was to set up an alternative Vaccine Advisory Committee that included a mix of skilled public health officials, scientists and medics.

The Foundation also turned its attention to the development of a second vaccine that had developed under the strengthened testing regime. However, the trajectory forged by Sabin faced a scarcity of resources in the wake of the Salk trials that forced its development abroad. Although Sabin found significant sums of money to fund research, the number of remaining vaccine volunteers in the US were limited and he had to conduct tests of his vaccine in the Soviet Union.

Testing in a different country emphasised the relative systemic components of successful innovation because the conditions in, and the requirements of, the Soviet Union were significantly different. The different decisions taken by the public health authorities suggest that the efficacy of vaccines is heavily dependent on the context and health system in which they are used. At this stage, the conditions of use were less shared than they were in the controlled development stages. The USA and USSR were different, but their laboratories were probably less so.

The imperative to develop a more thermostable poliomyelitis vaccine became more prominent as eradication strategies were being defined and efforts to articulate operational principles were made. But efforts to improve the thermostability of the Sabin vaccine were hindered by the use of other heat-labile vaccines that also depended on cold chain refrigeration, making it less likely that a thermostable poliomyelitis vaccine could liberate health systems of the need for sustaining cold chain systems. Moreover, at the other end of the temperature scale, new vaccine vial monitoring technologies could identify incidences of vaccine freezing as well as breaks in the cold chain. Whilst in some localised contexts, a thermostable poliomyelitis vaccine may have helped eradicate the disease, trajectories of technological development were more focussed on large global markets that fit within the technological system, and it was widely felt that the existing poliomyelitis vaccine did not need further development. Indeed the incorporation of heavy water

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received the Congressional Gold Medal and other such public medals, Sabin was lauded by fellow scientists, elected to the National Academy of Sciences and embraced by virologists worldwide.

isotopes was seen to be an additional problem, and potential benefits were being diminished by improvements to the cold chain and to vaccine vial monitoring systems.

This paper concludes that vaccines need to be tailored (often repeatedly) to their final operating environment in ways that are difficult to predict. This cannot be done on the basis of scientific deductions alone. Predictability and reliability are established through repeated but carefully managed empirical and experimental testing processes, which are exposed to increasing levels of complexity.[41] They are managed and co-ordinated by institutions and form part of their skilled routines, so that knowledge growth is shared and systemic.

Rosenberg's call for enquiry into this area of innovation remains highly germane. Greater attention to knowledge accumulation processes could help shift research to more readily solvable problems. Agency on its own cannot explain persistent, cumulative and systemic change - but exploring conscious and co-ordinated problem solving, and the resultant changes to understanding and know-how at the systemic level (rather than at the level of heroic individuals), is likely to reveal which fields of human endeavour respond well to R&D efforts. As this paper and others have shown, the notion of tracking multiple technological trajectories remains a useful tool when combined with a pragmatic lens (see for example papers that can be related to social and physical technology co-evolution, Blume 2005; Nelson 2008b; Blume and Tump 2010; Chataway, Hanlin et al. 2010).

For policymakers, this paper offers a basis for acknowledging that investing in dedicated testing regimes, alongside science investments, is an expensive and long term endeavour that involves strengthening institutions and developing skilled routines. For developing vaccines and products for neglected diseases, the capabilities of the both private and non-private sectors are often acknowledged as being necessary without detailing what those capabilities are. This paper has characterised some of these capabilities and explained why they need to be accumulated over time across a system of private and non-private actors. If potential problems in the accumulation of technological knowledge are not understood, anticipated and addressed, many of our social imperatives are unlikely to be met through sustained innovation.

[41] The extent of localisation in testing processes can be seen in a recent example where vaccine developers trying to offer a vaccine against 'holiday stomach bugs' requested clinical trial volunteers fly out to a holiday destination in an effort to simulate holiday behaviours and environments (Laurence 2009).

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