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Exploring dynamics and strategies of niche protection

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Exploring dynamics and strategies of niche protection

Abstract

This paper focuses on the processes and strategies of advocates and opponents in creating, maintaining and/or contesting the protective spaces in which 'urgently needed' but 'risky' pharmaceutical innovations are managed. Drawing on transition literature and recent work on niche protection, this paper adds to the conceptualisation and empirical grounding of niche protection by studying the dynamics of protection, in particular the different phases of niche development. Moreover, the links between niche protection processes and protection strategies pursued by niche players are explored. Dynamics of niche protection are explored in two case studies: the monitoring of treatments for HIV and of a vaccination against pandemic influenza. We conclude that niche protection depends on interactions between network building, empowerment activities and the construction of a positive niche narrative vis-à-vis anti-narratives raised by actors outside the niche. Furthermore, the nature of learning within a niche as well as the niche's robustness are determined by whether the strategies are predominantly accommodating or restrictive.

Keywords:
Protective space, niche, narratives, fast access to innovations, pharmaceutical sector.

1. Introduction

New pharmaceutical technologies often have a bicephalous character in that they tend to simultaneously produce both positive and negative effects. This dichotomy becomes especially delicate when the technology is perceived by a significant group of actors as being urgently needed, while its being introduced too quickly could endanger the thorough investigation of its negative impacts. This balancing act between providing early access and ensuring sufficient evidence regarding impacts is relevant for pharmaceutical innovations that aim to meet so-called 'unmet medical needs' (EMA, 2010). When clinical trials show that a

new pharmaceutical product has a promising safety and efficacy profile, patients and medical professionals often demand early access to this drug. In a sense, they act as 'lead users', being the first to face the need for an innovation and to have strong incentives to use it (Von Hippel, 1986).

One way out of this delicate balancing act is to introduce the innovative drug in a demarcated space. Such a space calls for tailor-made measures to be taken, e.g. setting up specific safety monitoring systems tuned to the disease or type of therapy. Therefore, the space is differentiated not only technically, but even more so in socio-institutional terms. The demarcated, specific character of the space often deviates from the regular safety monitoring of drugs and therefore sometimes needs protection. This article delves into the challenges of managing the protection of monitoring practices for pharmaceutical innovations that are perceived by a significant group of actors as urgently needed.

The introduction of novel pharmaceutical products is heavily regulated. Regular safety surveillance of drugs is regulated by a formal and standard set of procedures and rules. Before market introduction three phases of clinical trials need to show that the drug is sufficiently safe, efficacious and of good quality. After market introduction, monitoring continues through a standardised and automated way of collecting, validating and evaluating safety reports (cf. Fraunhofer, 2006 for a detailed overview), together forming a standard drug regulation regime.

The socio-institutional embedding of pharmaceutical products dealing with unmet medical needs deviates from this regime. To some extent, the term 'urgently needed' is subject to contestation, because actors can differ in the extent to which they demand fast access to a drug. At the same time, US and EU governments have instated specific pathways to regulate market introduction of 'urgently needed' products, e.g. in the form of accelerated approvals. In these regulations the term 'unmet medical needs' is codified. The Food and Drug Administration in the USA defines them as 'needs that are not addressed adequately by an existing therapy' (FDA 2006). The EU regulation explicitly points out specific disease areas to which these fast access regulations are applicable, viz. HIV, cancer, pandemic influenza and rare diseases (European Commission, 2006).

The accelerated procedures enable fast market introduction by alleviating pre-marketing testing requirements, such as passing over large-scale and expensive phase III clinical trials. In return, companies must commit to stricter post-marketing safety monitoring. This post-marketing surveillance, however, is less standardised and leaves room for flexible, disease- and country-specific solutions. These monitoring practices (and the related medical

practice of drug prescription and use) need to be protected from regular processes, otherwise the legitimacy of fast introduction can come under pressure. Although these arrangements can be regarded as exceptional, regulatory developments show that these protective spaces may become more prevalent in the future. In 2011, the European Medicines Agency (EMA) provided openings for a more flexible approach to drug approval in its Road Map 2015. One consequence could be that several approval procedures and post-marketing surveillance practices will co-exist, protected from the standard EMA drug approval procedure. Some scholars extend this idea and foresee a 'transformative' overturn of regulations at the regime level of drug development (Eichler et al., 2008). From a technology perspective, the advent of personalised medicine and pharmacogenomics might lead to more fragmented use of drugs, ending in a growing number of small disease categories, increasingly resembling the rare disease fields (Boon and Moors, 2008). These new developments indicate that more protective spaces of post-marketing monitoring are to be expected in the future.

Although US and EU regulations are in place to govern accelerated approvals of drugs, the way in which post-market monitoring should be designed is not dictated. Lead users, such as patients and medical professionals, attempt to organise these practices tailored to their particular (disease-specific) context. This article studies two disease areas, HIV and pandemic influenza, in which patients and medical professionals perceived an urgent need for new medicines and organised their own tailor-made or idiosyncratic monitoring practices.

To design and pursue these monitoring practices, there needs to be room for experimentation and improvement before they are strong enough to face the rigours of the rules dictating the dominant regime. Niches are considered to be protective spaces in which these experiments can be pursued. The 'niche' concept is part of the transition literature that conceptualises how new and emerging technologies are explored and developed against a backdrop of existing technologies and the associated socio-technical regimes and landscapes (Schot et al., 1994; Geels and Schot, 2007a).

This paper contributes to the existing literature on strategic niche management in two ways. First, it builds on recent work on niche protection by Smith and Raven (2012), in which they perceive niche protection as under-conceptualised. They identify three processes of protection: shielding, nurturing and empowering. The introduction of empowerment as a protective dynamic is interesting, as it emphasises the importance for niche actors to articulate narratives and the related perceptions of urgency as well as how they position their niche vis-à-vis actors who actively or passively contest these narratives. In the context of pharmaceutical innovation, this reinforces that post-marketing monitoring is a way to enable

the quick development and diffusion of drugs that meet unmet medical needs. This paper adds to the conceptualisation and empirical grounding of niche protection by studying the dynamics of protection, i.e. by studying the interrelations between the three protection processes over different phases of niche development. Niche formation processes have been recently studied (Hermans, et al., forthcoming), but the focus on protection is new. Since stakeholders proactively seek to organise or contest these niche processes, the links with protection strategies are also investigated. Second, this paper applies the concepts of niche protection to the field of drug development that is subjected to accelerated approval procedures. This provides us with the opportunity to augment the emphasis on technical artefacts being protected in niches with socio-institutional practices, such as post-marketing monitoring practices. In line with this, the following research question is answered: *How do interactions between protection processes influence niche development? And how do these processes influence niche protection strategies?*

This paper is set up as follows. Section 2 discusses the theoretical background of managing the protection of niches and explores concepts that can aid the study of the dynamics of and strategies for the development of these niches. Section 3 presents the methodology. Sections 4 and 5 provide the results for the HIV case and for the pandemic influenza case. The paper ends with conclusions and discussion (sections 6 and 7).

2. Management of niche protection

2.1 Innovating in protective spaces

Transition literature has focused on path-breaking innovations, mostly in the context of sustainability (Schot and Geels, 2008). These innovations are developed in niches protected from the selection pressures of the socio-technological regime comprising the prevailing, dominant technological design (Hoogma et al., 2002; Raven, 2006). Premature exposure to these pressures would probably mean elimination of the technological option in question (Rip, 1995; Schot et al., 1994). The characteristics of innovations, such as technical and design specifications of and demands for novelties, need to be gradually and interactively developed and become more concrete over time (Schot et al., 1994). Early-stage, bottom-up development in niches has been deemed successful when the niche practices have broken out into the dominant regime, changing the rules of this regime to suit the novel technology along the way (Geels and Schot, 2007a).

As part of this strand of literature, attention has been paid to the processes inside these niches (Raven, 2005; Ulmanen et al., 2009) and not so much to protection. Some classifications about niche protection have been made, e.g. that protection should be temporal and phased out in time, to avoid too generous support and lazy actors (Nill and Kemp, 2009). Protection and selection pressures should be regarded as part of a careful balancing act; even in heavily-guarded niches selection pressures are never far away (Geels and Schot, 2007b; Hommels et al., 2007). Even in these discussions, however, protection has been perceived as a given fact and has been under-conceptualised (Smith and Raven, 2012).

2.2 Protection processes in different phases of niche protection

Development of a specific new technology may benefit from temporal shielding from selection pressures by creating protective spaces or niches. Smith and Raven (2012) introduce three processes that need to be facilitated to provide sufficient niche protection: shielding, nurturing and empowerment.

Shielding is an outward-oriented activity, focusing on moderating or fencing off pressures presented by the selection environment. In this way it attempts to provide room for experimentation. Shielding can take an active form, i.e. when a protective space is created, or a passive form, such as when the space coincides with a pre-existing and low-profile setting. *Nurturing* refers to processes that support technology development within the niche. Earlier studies on niche dynamics uncovered three processes as being significant to internal niche development: stimulating learning processes, articulating expectations and building networks (Kemp et al., 1998; Schot and Geels, 2008).

Whereas shielding and nurturing have already been part of the transition literature vocabulary for a few years, the third process, *empowerment*, is new. Smith and Raven introduce empowerment, with which they mean efforts to increase the strength or competitiveness of a niche, to underline that niche protection is also a political activity by actors both within and outside the niche. For example, in the field of sustainability, niches dedicated to specific alternative energy sources are supported by public policy measures. In order to sustain this support, niche actors need to maintain a narrative to lobby their case. Actors outside the niche might contest these narratives or articulate anti-narratives. Using narratives, niche advocates constantly negotiate relationships between the content of the niche project and its wider context (Law and Callon, 1994; Smith et al., submitted).

While studying the three niche protection processes, the question arises as to what extent they differ during the development phases of niches, these being creation, maintenance

and phasing out. The *creation* of niches is associated with the articulation of expectations, promises and visions, leading to a shared agenda. In the context of this paper, examples include regulatory agencies expecting a novel pharmaceutical product to be able to meet unmet medical needs, and government agencies proclaiming the spread of a disease as an emergency situation. These expectations can even become 'performative' (Borup et al., 2006); they coordinate and motivate actors to act upon the shared agenda (Van Lente, 1993). In this way, stakeholders' engagements, mutual dependencies and a shared agenda might produce rhetoric and resources for the creation of niches (Schot and Geels, 2008). It is assumed that shielding measures are the processes most often introduced at this stage, i.e. in the form of agreements or resources made available.

In the *maintenance* phase, shielding can best be regarded as an activity organised in the early formation stages of a niche and continuing throughout its lifetime, e.g. governmental agencies providing resources to sustain a monitoring system. In this phase shielding is eclipsed by nurturing activities, i.e. developing and maturing the internal niche practices through learning and network building. For example, medical specialists, scientists and patient organisations interact more frequently and exchange knowledge about side effects and best monitoring practices. With regard to learning, we distinguish between learning about facts (first-order) and about values and norms (second-order learning; Grin and Van de Graaf, 1996). Empowerment activities also support niche maintenance because during this phase the niche narrative is expanded, e.g. based on the expectations articulated and the activities performed. Communicating the niche narrative to external parties might simultaneously incite antagonistic voices, e.g. people who find it an exaggeration to call it a state of emergency.

Finally, the last stage of the existence of a niche pertains to its *phasing out*. Niches vary in the degree to which their practices are institutionalised and the extent to which these practices reconfigure the regime. Niche practices can be developed in such a way that they 'fit into and conform to' the rules of the current regime. Another venue is that niche innovations generate significant changes at the regime level, in such a way that the rules of the selection environment are 'stretched and transformed' (Smith and Raven, 2012). In this article, the idiosyncratic monitoring practices can either be incorporated in standard drug surveillance or they can change the overall regime practices of drug regulation. Understanding the relation between niches and the regime is crucial in studying niche protection and as such is integral to our explorations.

2.3 Strategies for niche protection

In the context of niche protection, several strategies can be discerned, including arbitration of differing views, creating a platform for discussion, negotiating compromises, capturing others' perspectives and broadening the scope of the niche, or ignoring other voices. The dynamics of niche protection processes has repercussions for the ways actors deploy strategies to protect their niche. For example, network building can be pursued in different ways, leading either to homogeneous/concentrated or heterogeneous/dispersed networks, in turn producing either a restrictive or an accommodating strategy. This degree of 'openness', meaning the degree to which different views and interests are accommodated by the lead actors, is central to niche protection in the context of pharmaceutical innovations because these innovations are often subject to contestation and are traditionally coordinated by the closed medical community.

To show the influence of niche protection dynamics on strategies, two "extreme" poles are sketched in terms of openness: accommodating and restrictive strategies. Integral to this distinction between accommodating and restrictive is the notion of niche boundaries. By this, we mean that niche boundaries are the result of how actors within and outside niches position themselves and others, for example as expressed through narratives and anti-narratives. Articulating these narratives through protection processes, such as empowerment activities, leads to the opening up or closing down of the niche boundaries. In this light, niche advocates choose to follow either an accommodating or a restrictive strategy when managing their niche and their relations with the niche context. Table 1 shows this close relationship between the niche protection processes and the two strategic poles.

Table 1: Characteristics of restrictive and accommodating strategic niche management.

	Restrictive protection strategy	Accommodating protection strategy
Nurturing		
Network building	Concentrated and homogeneous network; no fit between included and excluded actors	Dispersed and heterogeneous network; fit between included and excluded actors
Learning	Fast first-order learning; little reflection as part of second-order learning	Slower first-order learning; much reflection as part of second-order learning
Articulating expectations	Robust expectations as guidance	Expectations in flux
Empowerment		
	No engagement with anti-narratives	Capturing of ideas from outsiders

The next section describes the methodology used to study various approaches to strategic management of niche protection in the context of monitoring urgent pharmaceutical innovations.

3. Methods

In order to study the management of implementing “urgent but risky” pharmaceutical innovations, two cases were selected. These cases were expected to differ from each other along the lines of the two strategies introduced in the previous section, in this way forming typical representatives of restrictive and accommodating protection strategies in the pharmaceutical sector. Following the US, the European Union introduced regulations to ensure fast access to novel products while at the same time calling for rigid targets on post-marketing surveillance. These special regulatory pathways are called conditional market authorisations, and approvals are issued under exceptional circumstances. They are applicable to pharmaceutical products that meet “unmet medical needs” and are in the interest of public

health (European Commission, 2006). This regulation focuses explicitly on three categories, namely: a) seriously debilitating or life-threatening diseases (e.g. cancer and HIV), b) medicines used in emergency situations (e.g. pandemic influenza), and c) drugs for rare diseases. From these categories two cases were selected: HIV and pandemic influenza[1]. Furthermore, these cases were expected to potentially illustrate an accommodating (HIV) and a restrictive (influenza) protection strategy. By covering the two "extremes" or "outliers" of the spectrum, the two cases present rich information on the dynamics and strategies under study (Eisenhardt, 1989).

The cases on HIV and pandemic influenza are studied in the Dutch context of post-marketing surveillance and drug use. The focus of this paper is not so much on the phase before market approval and the formal rules for fast approval, but on the implementation of the product innovation in combination with new and tailor-made safety monitoring practices. We focus on one country, the Netherlands, because a large part of the socio-institutional practices of drug implementation and post-marketing surveillance is country-specific. Furthermore, in the case of HIV many international initiatives originated in the Netherlands. Nevertheless, the pharmaceutical sector is an international business and has increasingly been regulated and monitored on an international level. International developments that typically influence national monitoring institutions were included in the analysis. The moment when public and private parties started to pay attention to pharmaceutical interventions was chosen as a starting point for the in-depth case analysis of niche protection processes and strategies. For HIV this means from the initial discovery of the disease in the early 1980s onwards, and for pandemic influenza from 2009 to 2010. The differences in duration of the cases was a possible signal of a distinction in the level of contestation of the niche's existence, as the size and urgency of pandemic influenza was more contested in a shorter period of time. However, it became clear that all cases on urgently-needed innovations concerned periods of high intensity in terms of contestation.

The analysis draws on four different data sources. First, 40 in-depth interviews with representatives of all relevant parties were conducted. These relevant parties included regulatory agencies, companies, patient organisations, payers, medical specialists, nurse practitioners, pharmacists, university researchers, and pharmacovigilance centres. It should be emphasised that the interview respondents were key informants within the two cases. To ensure reliability of data collection and analysis, all of the semi-structured interviews were audio-taped and fully transcribed for further analysis. These were then coded, based on the

[1] The rare diseases were excluded because they form a heterogeneous set of ailments.

dimensions mentioned in Table 1, which are further operationalised in Table 2. The participants consented to these recordings on condition of anonymity and restricted use for the purpose of this study. In the descriptions of the two case studies the respondents are made anonymous and coded as R1, R2, etc. During the interviews the respondents were explicitly asked to reflect on the role and anonymous statements of other actors in order to validate these statements. Because the range of potential interview respondents is confined, e.g. the number of HIV patient organisations is limited, we aimed to contact and interview as complete as possible a set of stakeholders. In most cases, initial contact was made through e-mail, although sometimes an introduction was made by a member of the multi-stakeholder workshop (see below) or other interview respondents.

Second, the interview data were substantiated and triangulated by desk research. The source literature included: 1) data on conditional approvals and approvals under exceptional circumstances (safety issues, speed of market access, etc.), based on studying the European Public Assessment Reports (EPARs) of drugs being developed; 2) policy documents, scientific articles, etc. which the interview respondents recommended; 3) a literature search of the Scopus bibliographic database using (a combination of) keywords, including 'conditional approval', 'approval under exceptional circumstances', 'early access', 'pharmacovigilance' and 'post-marketing surveillance'. This was performed in combination with keywords that restricted search results to the disease areas under study and the related pharmaceutical products.

Third, three multi-stakeholder workshops were organised, involving a wide array of stakeholders in the field of registration and post-marketing surveillance in the Netherlands. The participants included a doctor, an ethicist, industry representatives, representatives from patient organisations, the Dutch ministry of health, the pharmacovigilance centre, the Dutch Medicines Evaluation Board, and public scientific research funders.

Fourth, a news analysis was conducted to collect data on important events and statements by stakeholders. These data were needed to check the extent to which the interpretations made by interview respondents were supported by statements given by a wider range of actors. The newspaper articles were extracted from LexisNexis, a newspaper repository that provides access to practically all articles in Dutch newspapers from 1990 onwards. We searched five leading newspapers and three weekly opinion magazines that cover a wide range of social and political perspectives[2]. The articles were read and events and

[2] The sources were: De Telegraaf; NRC Handelsblad; AD/Algemeen Dagblad; Trouw; De Volkskrant; Reformatorisch Dagblad; Vrij Nederland; and Elsevier. Search terms for the HIV case: (((hiv OR aids) AND

quotations were selected. In the case descriptions, quotations based on the newspaper analysis are referred to with 'NP'.

All events and statements pertaining to monitoring of new drugs in HIV and pandemic influenza were extracted from the interviews, desk research, workshop transcripts and newspaper articles. This information was dated and included in an event history database (Van de Ven and Poole, 1990). The next step was to categorise the events into typologies based on the niche protection processes as introduced in section 2.2. To increase the (interrater) reliability of this coding exercise, the processes were specified in the form of dimensions and elaborations of these dimensions, as exhibited in Table 2. These dimensions were used as coding categories. Finally, the number of types of process events and statements was graphically laid out to show the prominence of each niche protection process in different phases of niche development, indicating the dynamics of protection processes in niches over time. The event history database also formed the backbone of the descriptions of the two cases, since its time-ordered collection of events and statements served as an historical account.

(bijwerking OR medicijn OR geneesmiddel)) and Date(geq(01/01/1990) and leq(01/01/2000))). This yielded 361 articles. For the period 1982-1989 we used quotes from the thorough historical overview of HIV in the Netherlands by De Mooij (2006) and our own interview results. Search terms for the influenza case: (((mexicaanse griep OR pandemische griep) AND (vaccin OR bijwerking)) and Date(geq(01/04/2009) and leq(31/12/2010))). This yielded 170 articles.

Table 2: Operationalisation of concepts.

	Dimensions	Description of dimensions
Shielding (Smith and Raven, 2012)	Active shielding	Introduction of resources (financial support) or legislation (rule exemptions)
	Passive shielding	Framed as pre-existing and low-profile activity
Nurturing – network building (Schot and Geels, 2008)	Concentration and interactions inside niche	Level of concentration and intensity of interactions
	Level of recruitment of actors outside the niche	Openness to network participation; active recruitment of excluded actors
	Degree of fit between included and excluded actors	Subjective evaluation of actors of niche inclusion
Nurturing – learning (Grin and Van de Graaf, 1996)	First-order learning	Developing demands, ideas and solutions
	Second-order learning	Developing underlying values and norms
Nurturing – articulating expectations (Van Lente, 1993)	Expectations	Changes in expectations and their concreteness
Empowerment (Smith and Raven, 2012)	Development of a niche narrative	Actors inside the niche articulating importance of the niche and its protection
	Relation to narratives of actors outside niche	Actors engaging in conversation with actors outside niche and reacting to anti-narratives

4. HIV: close-knit community with a strong narrative

4.1 Niche creation (1982-1986)

In 1982 AIDS arrived in the Netherlands. Since then the prevalence of the disease has grown rapidly, as has the attention paid to it. Action was needed because of its seriously debilitating, progressive and untreatable character. From the start, two types of actors attempted to dominate discussions: patients and medical professionals. First, the majority of patients affected appeared to be homosexuals, which caused unrest and panic in the relatively closely-knit community, largely concentrated in Amsterdam (R5; R7). Gradually, patients organised themselves, which led to a fragmented landscape of representative organisations, ranging from HIV-infected to seropositive, and from moderate (HIV Vereniging) to more radical (Act Up!). Although representatives of the homosexual community wanted to control the disease's spread, they were also concerned with avoiding social stigma. This position became clear in 1983 when the blood banks, which were unable to secure the quality of their products, wanted to exclude homosexuals from donating blood. Members of the gay community reacted against this because 'this would seriously damage the [emancipation] process in which they were engaged' (De Mooij, 2004). This discussion positioned them against the haemophiliac patients who feared for the quality of anticoagulants produced with HIV-infected blood. 'The interests of homosexuals dominated. Nobody wanted to run the risk of being accused of discrimination' (R31). Haemophiliac patients felt deserted by the government that 'let it all happen' (R1).

Medical professionals in Amsterdam formed the second group of influential actors. They worked in places to which patients turned first, such as at the municipal health service and the Amsterdam university hospital. Many aspects of the disease were unknown ('we were breaking new ground', R6), still there was a need for public communication and palliative treatment. Because of the unknown and imminent threat, informal meetings and bilateral contacts led to unorthodox solutions, such as dedicated information campaigns (1983), monitoring schemes of high-risk groups in the Amsterdam Cohort Study (1984 onwards), and the opening of a specialised ward at the university hospital with nurse practitioners or "HIV consultants" who specialised in supporting HIV patients (1986).

These two groups formed the advocates who attempted to define an HIV niche in which idiosyncratic solutions for monitoring safety could be initiated. These solutions were financed through both dedicated and ad hoc public funding, which can be regarded as active

shielding. Governmental agencies were fast to provide resources, not only due to the disease's severity, but also because they feared radicalisation of the patient community (De Mooij, 2004). There was also room for passive shielding in the sense that the prominent members of the homosexual community, who were regarded as well-educated and well-positioned (R2; workshop 1 and 2), were able to devote time and effort to organising idiosyncratic solutions. The same applied to the medical professionals involved: they were in the early stages of their careers and quickly assumed the monopolistic role of HIV/AIDS expert. This role was boosted by the concentration of HIV patients in Amsterdam and by the fact that in Amsterdam medical specialists had already been quite advanced in the haematology field (R29; R30). All in all, the creation of the HIV niche was characterised by a combination of active and passive shielding, largely driven by articulated expectations on fears for the unknown disease and for the possibility of large-scale diffusion: 'In the late 1980s and early 1990s patients were in great despair: people died in large numbers. People were frightened, and there was great pressure to do something about the disease' (R7). Empowerment played a part in the sense that the gay community propagated homosexual emancipation as a leading element in the communications and activities of the niche players. During this stage the first steps were taken to initiate a new scheme to monitor HIV. Activities only really gained momentum after the first drug entered the market.

4.2 Niche maintenance (1987-1996)

Scientists at public institutes and pharmaceutical companies diligently searched for treatment options. By following homosexuals (healthy, seropositive and HIV) and drug users, the Amsterdam Cohort Study had produced a large and high-quality scientific output. When the first antiretroviral drug, AZT, entered the Dutch market in 1987, two scientists who ran the cohort study approached the AZT-producing firm and asked to use the limited number of doses to set up a clinical trial. This collaboration formed the starting point of a series of post-marketing clinical trials. As short linkages existed between scientists, medical specialists and company representatives, and as the industry was unsure how to research and develop HIV drugs, there was ample room for investigator-initiated clinical trials. From 1990 onwards, these trials were coordinated by the National AIDS Therapy Evaluation Centre (NATEC), founded by the Amsterdam scientists and financed by the national government. The radical pressure group ACT UP! was instrumental in securing funds for the centre: 'When ACT UP! sent an angry letter and threatened with actions, NATEC was opened […] It is a disgrace […] AIDS is an emergency situation to which one should react quickly' (NP; also R6, R9).

Patients did not put innovation before safety at all costs. There are ample examples of patient organisations questioning accelerated approvals for fear of suboptimal quality of science and pharmaceutical products (Epstein, 1997; Goozner, 2004). The introduction of the antiretroviral drug AZT (1987), followed by ddI (1991) and ddC (1992), instigated an increase in the attention paid to side effects. AZT turned out to have severe side effects (R7), news of which 'travelled fast' through the close-knit network of patients, medical professionals, scientists and pharmaceutical companies: 'the HIV world was small and everyone knew each other' (R6). Patients and their representatives consistently depicted these drugs as 'poisonous' or 'AIDS on prescription' (NP; R7; De Mooij, 2004) and called for intensive monitoring of side effects. This led to the organisation of rich, tightly-connected arrangements of informal initiatives and organisations for monitoring safety. These arrangements grew organically from initiatives such as the Amsterdam Cohort Study. Moreover, discussions on drug safety were largely informal and took place in 'a bottom-up way in the surgery or the ward' (R5). The basis of these discussions was formed by close contacts between doctors and patients: 'Patients were very open. We smoked companionably during surgery visits […] We experienced a lot together' (NP).

The bottom-up and organic nature of these initiatives meant that safety monitoring in the field of HIV/AIDS was organised differently from the regular drug monitoring system. The niche advocates had proper incentives to differentiate. Among others, the additional money for cohort studies presented opportunities for the scientists involved to publish papers based on unique data, thus gaining recognition. This differentiation was eventually made permanent by an agreement between niche advocates, including the medical specialists, patient representatives, and the Netherlands Pharmacovigilance Centre Lareb (R11; R12; R16; workshop 2). This agreement flagged the described underlying niche maintenance processes: financial support for NATEC (active shielding), demands about safety and quick access to drugs (articulating expectations), and the forming of tight connections between users, medical professionals and producers (network building).

The network of niche advocates, which by then consisted of medical specialists and patient representatives, mostly situated in the Amsterdam area, learnt about safety monitoring along the way. Patient representatives talked like doctors and scientists, e.g. about data requirements in the context of clinical trials and about drug characteristics such as how they work and how adverse side effects should be perceived. A patient representative discussing an international cohort study claimed that 'the []-study has a few limitations, such as the diversity of patients included. There is a need for validation through an RCT or a second

cohort study' (R9). Epistemologically, patients aligned with medical professionals on how to collect and analyse data, and how to take action based on these data. Patients had a high level of access and control over post-marketing surveillance through the personal contacts they maintained with the initiators of these post-marketing efforts, e.g. through active involvement in reporting adverse drug reactions (De Langen et al., 2008) and discussions on when to start AZT treatment (NP). Patients also had an incentive since they thought that 'others, even including doctors, were not interested in discerning the cause of their physical deterioration: whether it was the use of medicines or the disease itself' (NP).

This combination of network building, the articulation of expectations and (second-order) learning fuelled the narrative that reinforced the niche boundaries and positioned the outside actors. The latter took form in three types of confrontations. The first was "consumer clubs": patients urgently needed new medicines and wanted to take risks. They did this by demanding access to medicines that were still being tested in clinical trials (NP) or by opening illegal routes to obtain medicines. These illegal routes became heavily contested within the medical and patient communities: they were not against illegal or risky use as such, but they wanted the effects to be monitored (NP). They wanted to be involved, fearing that these "consumer clubs" would 'go underground' (NP).

Second, there were confrontations with alternative or traditional medicine practices that reacted against the 'mathematical ways' of Western medicine (NP), thus attracting a lot of attention. The medical and patient communities dissociated themselves from these practices. The medical professionals were most articulated about it, calling the promotion of these alternative views as 'folklore', 'hot air' or even 'criminal' (NP).

Third, the patient movement was dominated by homosexuals. Fear of stigmatisation of homosexuals because of AIDS led them to proactively dominate certain areas of AIDS policy, such as communication about prevention (De Mooij, 2004). This dominance resulted in other patient groups being less well heard. Examples include drug abusers (who were regarded as "little brothers"), immigrants from low-income countries, and seropositive people who had slightly different interests in disease communication and prevention (NP; R1). In this period the confrontation between the niche advocates and the haemophiliac patient group flared up again over the latter's wish to receive compensation from the government for its not being conscientious enough with the quality of donor blood, as this portrayed haemophiliac patients as 'innocent victims' compared to other patients (NP).

The emphasising of the niche narrative reached its summit during the introduction of protease inhibitors as a promising new drug class in 1996, which marks one of the most

striking and discussed episodes in the Dutch HIV history. After admittance in the US, the drug awaited European approval. This limited the market access of the drug to a great extent: although off-label use is allowed under certain conditions in the Netherlands, reimbursement for the drugs formed a problem. The AIDS charity fund Aids Fonds and prominent medical specialists zealously advocated for reimbursement for the drug: 'HIV patients don't have the time to wait for bureaucratic decisions' and 'there is a medical need' (NP). They had several meetings with civil servants from the ministry of health. During one of them the minister of health attended. She was a physician by training and had personally studied the scientific papers before the meeting. Based on that information, she decided to act against the recommendations of her civil servants and created a special reimbursement scheme (R6; R13; NP). 'The civil servants were really sputtering but then she suddenly said: "but you don't have AIDS, [name of civil servant]" ' (R6). In return, the minister insisted on a closer surveillance of HIV drugs use. An observational cohort project (the Athena project, later the Stichting HIV Monitoring) was created, in which all patients were included and monitored.

4.3 Niche phasing out (1996-now)

The introduction of the new class of drugs, protease inhibitors, created the possibility to prescribe combinational therapy that appeared effective in suppressing – but not curing – the HIV virus. AIDS became a manageable disease, which posed new challenges such as therapy compliance, especially in the face of 'patient-unfriendly' therapy regimes that 'are hell' and 'ruin your social life' (NP). Also, as people with the disease lived longer, this exposed new side effects such as cardiovascular problems and abnormal fat accumulation (lipodystrophy), leading to a 'renewed flooding of hospitals' (NP) and new monitoring initiatives such as the European Data Collection on Adverse Events of Anti-HIV Drugs (R12).

These new developments fit into the existing niche practices. Discussions about adverse drug reactions and drug usage largely remained within the surgery, in interactions between medical specialists, nurse practitioners and patients (R5; R9). News about side effects circulated quickly: nurses had an e-mail service and medical specialists called each other. Only occasionally did doctors report side effects through regular channels (R7; R10). In other words, the special arrangements had become more formalised but remained different from the regular safety monitoring practice (R10; R16). Network building and learning followed a similar pattern, becoming larger-scale and more structured.

Pressure from actors outside the niche gradually subsided, mostly because actors became part of the niche and adopted the narratives of the niche. This was the case with

politicians and policymakers. Other actors, such as medical specialists in cities outside Amsterdam, became involved because the geographical reach of the niche widened. Partially, this happened because of the sheer presence of HIV patients outside Amsterdam, and partially because these medical specialists were included for strategic reasons. Other patient categories that were originally excluded from the niche were not potent or persistent enough to resist or influence the niche boundary. Strategies for empowerment were not very forceful. The establishment's fear that patients would radicalise was always close to the surface, and this was seen as a powerful weapon for the patient community (R4). However, they were quickly taken up by the consultative ("polder") structure of Dutch policymaking, and aggressive activism made no headway (De Mooij, 2004). There was also no need for forceful empowerment, because the abovementioned anti-narratives were either articulated by far less powerful actors, or by actors whose narrative could easily be included in the niche's main narrative. The latter then led to capturing these actors in the network of the niche.

At the same time, the separate status of the niche, and thus also niche narrative, became the subject of discussions. The special status of HIV/AIDS was criticised in Dutch newspapers as early as 1992: 'The amount of money reserved for AIDS, if one looks at severity and incidence, is not in proportion to cancer and rheumatism'; 'The medical profession is vexed with the amount of attention paid to AIDS' (NP). In the same vein, some commentators disapproved of the 1996 reimbursement debate: the decisions were made 'miraculously quickly' and 'lobbying was uncritically received' (NP). Several stakeholders even began to question the degree to which the medical need of HIV patients was still unmet (R5; R10; R14).

Especially after the introduction of two drugs in new antiretroviral classes in 2007 and 2008, risk aversion regarding HIV medicines seemed to grow. The need for novel drugs has been decreasing. Recently-approved medicines are only used if other drugs fail and if they show an apparent increase in user-friendliness (R5; R10). Medical specialists and nurse practitioners claim that more attention should be paid to the safety of new drugs: 'Careful consideration should be given to whether the accelerated approval of a novel drug is ethically justified' (R5).

Despite questions about the need for protection, there has not been any serious political or policy discussion about this topic. Politicians and policymakers have been part of the HIV niche network for years. 'Regulators have not become more restrictive. This might be related to the credibility that has been built up over the years' (R12) by companies, regulators

and patient organisations. Therefore, it seems that the narrative of niche protection is slightly changing without affecting shielding or nurturing processes.

4.5 In sum

The HIV case shows that a community of niche advocates, consisting of medical professionals and patients, dominated the balancing between quick access to drugs and the establishment of an elaborate set of safety monitoring initiatives. Through protection measures, this set of initiatives was different from regular monitoring. Figure 1 depicts the dynamics of protection processes based on the coding of events, i.e., the prominence of each niche protection process in the various phases of niche development.

Insert Figure 1 about here.

Figure 1: Number of events per year, coded by niche protection processes over three phases of the HIV niche development.

5. Pandemic influenza: outside pressure on niche narrative

5.1 Niche creation (April – May 2009)

In April 2009 the first cases of what would later be known as the Mexican flu, or influenza A virus subtype H1N1, were discovered in Mexico. The virus rapidly spread, and in June 2009 the World Health Organisation (WHO) declared the influenza as pandemic. For years virology experts had warned health authorities that the ever-changing genetic make-up of viruses would imply a statistically certain future influenza outbreak resembling the severity of the 1918 Spanish flu. Experts and authorities had already started planning for a possible new pandemic after the avian influenza outbreaks in Asia at the end of the 1990s (EU, 2001; Fedson, 2004; Stephenson et al., 2004; WHO, 2003). One example of the preparations is the guideline produced by the European Medicines Agency (EMA) in 2004, which described the way in which influenza vaccines could be approved in an accelerated fashion (EMEA, 2004). Pharmaceutical companies started to work on the development of vaccines, the first of which were approved in 2008. In the Netherlands a set of strategies was developed to deal with a viral outbreak. Part of these plans included the foundation of the Outbreak Management Team, alongside several departmental steering committees.

With the arrival of the Mexican flu in the Netherlands at the end of April, the Outbreak Management Team convened for the first time. In the media a prominent virologist warned for a large number of casualties: '50 million people died from the Spanish flu, which started in the same way' (NP; R22). During this early May 2009 period the messages about the seriousness of the influenza were ambiguous. US figures show that the influenza was rather mild, and commentators mockingly talked about it as a 'CNN-outbreak' (NP). At the same time, the Dutch Health Council, consisting of medical scientists and practitioners, underlined the risks and recommended vaccination for certain high-risk groups (The Health Council of the Netherlands, 2009). The minister of health followed this advice, acquired 35 million vaccines and began to plan the vaccination. The Health Council also explicitly articulated the need for a system to monitor side effects.

The organisations and people involved with managing the vaccination operation had two anxieties. First, they wanted to avoid a repeat of the low vaccination coverage seen a year earlier with the human papillomavirus (HPV) vaccination of female adolescents in the Netherlands. 'The HPV campaign was seen as a predecessor of the flu campaign' (R21). This vaccination campaign started discussions about the necessity and risks of these vaccines. Critical, Internet-based groups were founded that produced countervailing information against what they saw as 'imperative' demands made by the Dutch government to take the vaccination (R20). Second, due to the accelerated character of approving the vaccines and previous experiences with influenza emergencies, safety issues could not be ruled out altogether. Especially the increased incidence of Guillain-Barré syndrome following influenza immunisation during the 1977 swine flu pandemic was cited (NP) as a reason to take adverse reactions to influenza vaccinations seriously. Both anxieties led health experts to underline 'the importance of safety monitoring' (NP).

The National Institute for Public Health and the Environment (RIVM) had always been responsible for managing the vaccination programmes and had an elaborate monitoring system in place for non-emergency vaccinations. However, both in informal departmental deliberations and in the media, the interlinked responsibilities were questioned at that time: 'RIVM always steamrolls all objections; trust in vaccination is not helped by one institution being responsible for planning, execution and evaluation' (NP). The RIVM agreed but responded that 'we should not try to come up with new pathways in times of emergency' (NP).

The ministry responded to these pressures by delegating this task to the Netherlands Pharmacovigilance Centre Lareb. Lareb originated from a local initiative but had gradually

grown into a national platform. It perceived itself as ‘bottom-up, scientifically-engaged, no-nonsense and independent’ (R11). Others acknowledged this independent character (NP). For years, Lareb had been responsible for monitoring drug safety, but its remit did not include vaccinations. The organisation took the influenza pandemic as an opportunity to enter this subfield of safety monitoring, in the meantime introducing some novelties in post-marketing surveillance. Lareb proactively made a scenario of how to perform post-marketing surveillance in the case of a pandemic, but there were still issues that needed to be sorted out (R18).

In sum, the implementation of pandemic influenza vaccination in 2009 was the first time the Netherlands needed to respond to an epidemic on a large scale and in a short period. Although there had been preconceived ideas and scenarios as to how to deal with a pandemic, and RIVM had had an outbreak management response structure in place (R23), the governance of immunisation needed to be worked out. The regular circuit of influenza experts and organisations specialised in vaccination could be regarded as close-knit. ‘The vaccination world is quite closed, with small groups of experts who all know each other very well’ (R11). The sense of urgency drove these experts into each other’s arms in practical form, through a ministry-coordinated “task force”. Still, the constellation was tentative and fragile because of the immature and contested nature of its organisation. These practices can be regarded as being set up in a protective space. The ministry played a central role and coordinated the niche in a top-down way, among others by providing resources to shield the niche from outside pressure. Moreover, prominent scientists and civil servants canvassed the severity of the pandemic, by forcefully articulating expectations about the need for safe vaccination.

5.3 Niche maintenance (June – December 2009)

During the summer it became clear that the pandemic was milder than expected and ‘not any different from a seasonal flu’ (R25). This posed the ministry with the issue of whether to continue preparing for vaccination. The voices of the niche advocates also became muffled, even to such an extent that they came personally under pressure as ‘scare mongers and doomsayers’ (NP). Moreover, the press suspected one of the prominent niche advocates of profiting from his ‘influenza prophecies’ through the shares he owned in several companies. The contestation of expectations led to questions about the need for and safety of vaccination. An editorial in The Lancet again drew parallels with the 1977 pandemic in the US and warned against ‘accelerated safety trials under time pressure’ (NP). Dutch experts underlined this in the media: ‘You give something to people who are not ill and certainly don’t want to become

ill', but recognised that 'absolute safety is a utopia' (NP). They also warned for 'indifference […] we're faced with the difficult situation that the general public is fed up with the influenza even before it has really hit the Netherlands' (NP).

Meanwhile, Lareb actively took up its new task and engaged in 'intensive contacts' with RIVM, the ministry of health and the two pharmaceutical companies (R23; R24; R25), as agreed upon through mutual consent (R25). The government was convinced that adverse drug reactions were best monitored using a spontaneous reporting system (Van Puijenbroek et al., 2010), complemented by additional large-scale studies as requested by EMA as part of the accelerated approval procedure. Issues they needed to deal with were the speed of monitoring, 'given the large number of people who had to be vaccinated in a short period of time' (Van Puijenbroek et al., 2010) and 'noise' in the reporting (NP). This resulted in the implementation of an "intensive monitoring" system on which Lareb had worked since 2006 but which would then be applied in a real-life situation, which practically meant that they needed to "learn on the job". The system consisted of web-based questionnaires that focussed on specific, spontaneously reported side effects. The resulting reports 'were checked on a daily basis for seriousness' (R18), allowing the opportunity to approach the reporter or medical professional for additional questions. By actively linking reports with the vaccine serial numbers, batches could be withdrawn if needed. All parties involved in the vaccination process, including the companies, stimulated the vaccinated people to report eventual side effects through Lareb.

The narrative proclaiming a need for immunisation was confronted with anti-narratives that gradually gained momentum, especially in social media, in the period leading up to November 2009 (NP). Traditional media also received e-mails daily and reflected on them occasionally (NP). These critical voices can be categorised in several groups. First, a few prominent scientists voiced concerns about the efficacy and safety of the vaccines, e.g. based on large-scale meta-studies. They also criticised the close-knit character of the 'nerd community consisting of people who gradually [would] become' victims of "groupthink" (NP).

Second, some groups had resisted the National Immunisation Programme for years, such as religious groups: 'The objection concerns the principle that vaccines pre-empt divine providence' (NP).

Third, one prominent critical group emphasised the freedom of choice of individuals. When a decision was made to start vaccination, all uncertainties were set aside in order to maximise the vaccination coverage level. The government 'always communicates in an over-

simplified way about the safety and effectiveness of vaccines' (R20). This leaves no room for individual, autonomous choice, which 'does not correspond with uncertainties that prevail amongst scientists and medical professionals about the vaccines' (R20). This group aimed at 'well-considered information' (NP) about vaccination.

Fourth, another prominent group centred on an alternative, holistic approach to healing, i.e., 'the best vaccine is the one you make with your own body' (R26). Vaccines were regarded as poisonous, and as 'the cause of a range of diseases including autism and MS' (NP). This group was very much concerned about certain ingredients of the vaccine, including thiomersal and squalene (NP).

Finally, some anti-narratives concerned conspiracy theory perspectives: 'a group of powerful men want to decimate the world's population', 'the US Army create vaccines as biological weapons of mass destruction', etc. (NP). There is 'no trust in experts […] They are merely there to gain money and power […] You need to research it for yourself' (NP). Other anti-authoritarian or 'concerned citizens' hooked up with dedicated anti-vaccination groups. They even went to court to force producers to reveal the vaccine's composition (NP).

These five types of critical groups were quite successful in attracting media attention and influencing people's opinions. Most groups arose 'quite spontaneously' and bottom-up; 'there was no real plan' (R26). The interactions were largely organised through the Internet on blog websites where people could leave their comments and react to each other. Some notorious Dutch websites published explicit pictures of victims of HPV-vaccination, and the monitors of these websites posted messages and articles which were inspired by information and experiential stories they received via e-mails.

Although the five groups shared their opinions of objecting to vaccination and could benefit from joining the bandwagon to 'articulate their longstanding suspicions' (R20), there was no shared spirit. For example, people involved with the fourth group 'found the conspiracy theories to be too much' (NP). Therefore, the anti-narrative was heterogeneous and the five groups differed in the extent to which they disagreed with the niche players. On an epistemological level, the critical groups were rather mild in their criticism of monitoring activities. They acknowledged the existence of Lareb, emphasised that 'people should report side effects to this organisation' (R20) and praised its transparency. At the same time, they thought that 'not all reports were registered' (R26) and that 'only the tip of the iceberg was reported' (R20). They claimed that elements of safety monitoring were ignored (R20; R26). Moreover, they performed post-marketing surveillance themselves: they collected articles and experiences which they mainly received via e-mails, they reacted to publications of post-

marketing studies, and they studied side effects in order to include them in their communications. They had their own safety monitoring system ('I can draw on a network of experts from all over the world'; NP) that had the same approach in mind as professional monitoring ('In my latest communication I used 352 scientific references'; NP).

The lacking sense of urgency that lasted during summer and early autumn was reversed in the beginning of November 2009 when a three-year-old girl died. Suddenly the call for vaccination became louder; two-thirds of Dutch parents wanted their children to be vaccinated (NP). This 'shift in public opinion' (NP) coincided with reflections in the media on the relationship and communication between niche advocates and critical groups. The niche advocates accused the critical groups of causing confusion, being unapproachable, and being critical just as a knee-jerk reaction to the government. 'It is like a belief; they know blindly that they are right… discussions are pointless' and 'dangerous' (NP). During the few face-to-face discussions, the niche advocates aimed at conviction and perceived that they 'took the critical voices seriously' (workshop 2). In parallel, especially for the benefit of the general public who had difficulties making up their minds, niche advocates, amongst others the minister of health, advertised the necessity of vaccination, often referring to 'banishment of other infectious diseases like polio' (NP). Moreover, they compared the risks of adverse effects of the vaccines with risks associated with 'crossing the street' (NP). At the same time, niche advocates tried to marginalise the anti-narratives in their firm belief that the anti-narratives 'could lead to irresponsible actions and even deaths' (workshop 2). The critical groups complained about the lack of transparency of governmental agencies and the fact that the niche players 'did not take them seriously at all and thought that their remarks were not sound enough' (R20; R26). Besides, they regarded the communication about the vaccination as being organised in a 'classical and old-fashioned', top-down and paternalistic way (R23).

Since the purchase of the vaccines, a large range of organisations had prepared the vaccination campaign that took form in two rounds, late November and mid-December 2009. Lareb published results, based on a survey completed by 2500 people in three days, revealing that 27% experienced minor inconveniences. The Centre also received 718 safety reports, mostly about children with fever. A week later this was confirmed by international data. After thorough investigation, Lareb negated the association between the death of two young children and immunisation.

5.4 Niche phasing out (December 2009 – December 2010)

The vaccination period spanned just two months. During this time the critical groups obtained sufficient media coverage to attract quite a bit of attention. After this period the general public's interest in the topic and niche activities quickly subsided (NP). The questions about the need to purchase the vaccines, the communication plans and functioning of experts led to critical evaluations by various niche players, such as the ministry of health and the EMA (NP). Immediately thereafter, the evaluation of vaccine monitoring once again became relevant because of Q fever outbreaks. The role of Lareb was rather favourably reviewed, since the number and quality of reported adverse events was regarded as high (Van Puijenbroek et al., 2010). This made it easier to effectuate the earlier plans for the transfer of vaccine safety monitoring from RIVM to Lareb. This division of tasks and the increased role for Lareb led to the solidification of the responsibilities of the niche actors.

5.5 In sum

The influenza case shows how a closed niche around vaccination monitoring, consisting of organisations that had been used to follow longstanding rules in contexts of emergency situations related to infectious diseases, broke away from these rules and rebuilt a new network for implementing and monitoring vaccinations. Protection processes were needed to sustain this rebuilding, which was especially critical because of time and anti-vaccination pressures. Figure 2 exhibits the dynamics of protection processes, based on the coding of events.

Insert Figure 2 about here.

Figure 2: Number of events per year, coded by niche protection processes over three phases of the influenza niche development.

6. Concluding remarks

This article has focused on the processes and strategies of advocates and opponents in creating, maintaining and/or phasing out the protective spaces in which the implementation of innovations that are perceived as 'urgently-needed' and 'risky' is managed. A balancing act ensues between fast access and implementation on the one hand, and a careful monitoring of safety and efficacy on the other. The cases presented illustrate novel monitoring practices,

following the accelerated introduction of pharmaceutical products organised in protective spaces.

6.1 Comparison of cases

The descriptive analysis of the development of the *HIV niche*, supported by Figure 1, shows that active and passive shielding was a main activity during niche creation, combined with the articulation of expectations, i.e., fear of uncontrolled diffusion, and tentative network building. In the niche maintenance phase, active shielding and the articulation of expectations were complemented with nurturing activities such as further network building and learning. These activities confirmed the major narrative of the niche, thus legitimising shielding and empowerment processes. These empowerment activities were especially aimed at the anti-narratives. Some groups, such as intravenous drug abusers and haemophiliac patients, were excluded and not represented in the niche. They lacked the power to influence the outside boundaries and the legitimisation of the niche. Empowerment efforts and protection strategies, therefore, had the character of simply capturing outside actors and dragging them into the niche, only changing the niche's narrative on minor points. Other strategies included ignoring anti-narratives, "overwhelming" anti-actors or threatening to radicalise or drop out of vital policy processes. Due to these inclusion strategies, the size and scope of the niche broadened in the phasing-out period. Nurturing led to solidification of the niche activities and shielding remained in place, even despite diminishing levels of unmet medical need, which might question the need for protection (Hommels et al., 2007).

Figure 2 and the descriptive analysis of the *pandemic influenza niche* show that the institutions involved in vaccination needed to respond to an emergent pandemic for the first time since they had redrawn their operations during the avian flu a decade earlier. Still, the reorganisation of the implementation and monitoring structures had not been completed and would be tested for the first time in a real-life situation. This led the old regime players, and especially the ministry of health as prime actor, to break open existing monitoring practices and include new players (Lareb), which called for experimentation without the opportunity of failure. In other words, they perceived that a protective space was needed to set up and test these idiosyncratic practices in a safe and swift way. Niche advocates, i.e. the ministry of health and several vocal scientists, introduced resources such as shielding and supported them with forceful expectations. After the creation of this niche, the expectations and the related niche narrative came under heavy attack from a heterogeneous set of critical grassroots

groups. Their anti-narratives, i.e., flu is not serious or vaccines are not safe, were picked up by the press and the public. The two narratives were regarded as irreconcilable, which led to antagonistic expectations and allowed no room for including outside actors in the niche network, not even for strategic or rhetoric reasons. The empowerment activities were not aimed at capturing critical outsiders or broadening the niche network. During vaccination a high degree of first-order learning occurred; especially Lareb learnt "on the job" in preparation for and during the vaccination period. The phasing-out period of niche development was dominated by evaluating and rethinking niche practices. Some novel practices, such as the role of Lareb, were solidified, meaning they were adopted as part of the regular vaccination regime.

6.2 Conclusions

At this point we are able to answer the first part of the research question: *How do interactions between protection processes influence niche development?*

First, shielding seems to be a necessary precondition in order for nurturing and empowerment to take place and forms a prominent activity in the niche creation phase. In later phases, shielding legitimises nurturing and empowerment activities, while (in return) these two processes endorse shielding. Only when nurturing and empowerment falter does shielding come under pressure.

Second, the major activity regarding niche protection occurs in the interaction between nurturing and empowerment. Both processes work toward the formation of a narrative that legitimises niche protection. The expectations and learning about innovative safety monitoring are translated into a narrative that niche advocates use when they interact with actors outside the niche during their empowerment work. Both cases show combinations of visions that are unchangeable, e.g. fear of stigmatisation in the HIV case and fear of diffusion in the influenza case.

Third, empowerment draws close to the network building aspect of nurturing, as actors who share the agenda of technology development try to enlist or inspire other actors to join the niche's network. This network building recruits actors who can contribute to the formation and functioning of the development of an innovation because they provide resources, legitimacy or social capital in terms of facilitating interactions. Slight changes in the niche narrative, as the HIV case showed, are taken for granted.

These three insights add to current conceptualisations of niche protection, e.g. in Smith and Raven (2012), by showing interactions between the niche protection processes and

separating the influence of these processes over three phases of niche development. This adds a dynamic character to the conceptualisation of niche protection in the field of pharmaceutical innovations. Moreover, this article provides useful insights into how to analyse empowerment activities in and around niches, especially in the context of contested pharmaceutical innovations.

The second part of the research question deals with the link between these protection processes and strategy: *How do protection processes influence niche protection strategies?*

First, strategies to manage protection concern the relation with the regime level. In the HIV case it turned out that the niche did not change regular safety monitoring and captured a separate position in the monitoring regime. In that sense, the niche applied neither to the concept of 'fit and conform' nor to 'stretch and transform'. The vaccination case showed that the pandemic influenza period was a short, experimental excursion from the regular vaccination monitoring regime, during which new practices were tested and evaluated and then taken up in that regime. Thus the niche practices conformed more than really transforming the regime. In the context of niche-regime interactions, the HIV case is particularly interesting because it shows a middle course between conforming to and completely overthrowing existing regime rules. As the HIV example shows, one can argue that protections can also institutionalise and lead to a slightly reconfigured regime. This finding enriches the spectrum of available niche-regime interactions (Smith, 2007).

Second, the strategies relate to competing and criticising narratives. The cases show different ways to deal with these anti-narratives. In the HIV case, niche players attempted to capture outsiders by minor narrative change or by "overwhelming" them, ignored anti-narratives and threatened to radicalise or drop out of vital policy processes. In the pandemic influenza case, niche players showed no engagement with anti-narratives.

Although the strategies displayed in the two cases do not neatly align to one of the two extreme poles of restrictive versus accommodating protection strategies (cf. Table 1), the HIV case leans more towards the latter. The accommodating protection strategy focuses on reflective second-order learning, slower first-order learning and capturing ideas and actors from outside the niche. The pandemic influenza case was characterised by niche players maintaining a low degree of interactions with outsiders, even ignoring them. Their focus was neither on reconciliation or convergence nor on capturing critical outsiders or broadening the niche network. The case bends more towards the restrictive protection strategy with robust expectations, fast first-order learning, and no engagement with the anti-narratives.

This study points at possible advantages and disadvantages of both strategies. The upside of restrictive strategic niche management is the fact that the small core group of included actors can learn, implement and set up monitoring quickly. Innovations can be quickly implemented, together with socio-institutional measures that guarantee safety. The downside is that the excluded actors are not taken into account or are regarded rather late, leading to surprises, e.g. lower vaccination coverage rates, and in the long run less robust niche narratives (Rip et al, 1995). Moreover, the literature on learning also hints at the dangers of seeking premature consensus and compromises, as this leads to 'killing' of fresh ideas and to tunnel vision (March, 1991).

6.3 Limitations and outlook

The research methodology has some limitations. The major issue concerns the retrospective nature of at least the HIV case, which might have led to the re-evaluation of history by interview respondents and workshop participants. We tried to ameliorate this issue by providing the timeline of major developments as a backbone and as a mnemonic device. Furthermore, coding events and especially dividing the timeline into three phases of niche development is subject to investigator judgement. We dealt with this through independent coding and by comparing codes, which increased the interrater reliability. There were difficulties especially in discerning the three niche protection processes, e.g. how to discern expectations from empowerment, which has actually been inherent to the conceptualisation of protection so far.

The research findings in this study should be understood within the context of the cases, which might diminish the external validity of the findings. Examples of this contextualisation include the emancipation of homosexuals (HIV case) and the growing role of social media and a social movement towards anti-elitist sentiments (influenza case). Furthermore, the cases focus on the Dutch post-marketing monitoring system, which might be atypical because of the politico-economic tradition and governance culture of discourse-based decision-making. This led the HIV patient organisations, for example, to be corporatist/participatory rather than confrontational/activist. These backgrounds have been taken into account as much as possible.

In sum, this paper increases our understanding of the management of the implementation of innovations in the field of drug development subjected to accelerated approval procedures. This study characterises different processes that support niche protection and uncovers

patterns between these processes as well as differences in these processes in the various phases of niche development. Accordingly, this study contributes to conceptualising the dynamics of and strategies for inducing niche protection. As was mentioned in the introductory section, in the pharmaceutical sector regulators regard drug safety monitoring tailored to specific diseases or drugs as a way to organise arrangements for monitoring in the future. Also technological developments, such as personalised medicine as a result of pharmacogenomics, might lead to diversification and segmentation of these socio-institutional practices for monitoring. This could result in a distributed set of tailor-made niche protection practices, thus changing the monitoring regime. However, the regime could very well remain applicable to a substantial part of the total pharmaceutical sector, thereby leaving room for the co-existence of practices and strategies. This means that players in the pharmaceutical sector, such as companies and regulators, who have increasingly been organised on an international level, might need to take idiosyncratic, contextualised practices of post-marketing monitoring into consideration and could benefit from doing so.

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