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On scale work: evidential practices and global health interventions

Véra Ehrenstein
Daniel Neyland
Sociology, Goldsmiths, University of London

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Corresponding author

v.ehrenstein@gold.ac.uk

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On scale work: evidential practices and global health interventions

Véra Ehrenstein, Daniel Neyland
Sociology, Goldsmiths - University of London
New Cross, London, SE14 6NW, UK
v.ehrenstein@gold.ac.uk

Abstract

Scalability can be understood as the ability to expand without changing. Yet expanding an intervention to a global scale, we suggest, is a significant and difficult accomplishment. In this paper we propose to explore the kind of evidential exigencies that this accomplishment involves. To do so, we focus on the field of global health and examine how child immunisation against the pneumococcus bacterium has been scaled up in low income countries. The paper first attends to initial epidemiological scrutiny that revealed the existence of a large-scale public health problem and the possibility of an expandable solution (vaccination). It then describes the set-up of a funding arrangement using overseas aid to purchase vaccine doses manufactured by pharmaceutical companies, before paying attention to various frictions that affect the widespread use of pneumococcal vaccines. In these different moments through which scalability is accomplished, always partially and temporarily, we show that a dual activity can be witnessed, a pivoting between referential work and forward projection. To conclude, we suggest that scalability is more usefully approached as a form of expansion that is always attentive to the possibilities of change.

Keywords

Scale work; scalability; evidential practices; global health; vaccines; markets

Introduction

Tsing (2012) suggests that the modern world is characterized by ‘the triumph of technical prowess over nature’ (p. 513), a triumph that depends on forms of ‘scalability’. Scalability does not connote an ability to use scale, but rather to expand without changing. In our research into interventions using overseas aid to improve health across the world, this move to expand without changing is a central issue. It involves composing, successfully holding in place and navigating all manner of vicissitudes through scalability and, in the case examined here of child immunisation, it is crucial to ensuring that the purchase of vaccines is funded, that vaccination actually takes place and that effects on health can be assessed. Scalability, we suggest, requires careful management. In particular, this paper will show that various evidential practices (vaccine trials, epidemiological modelling, cost assessment, impact studies, etc.) must be mobilized to accomplish an intervention such as child immunization in a viable way and on a large-scale, to introduce molecules into millions of human bodies and durably transform their microbial flora so as to prevent diseases: an attempt to utilise technical prowess to triumph over nature.

Over the last three decades, overseas aid spending on health has experienced a significant increase (from an estimated total of 7.2 billion dollars in 1990, to 11.7 in 2000 and 36.4 in 2015; Dieleman, *et al.*, 2016).ⁱ This increase has been associated with particular organizational forms (public-private-partnerships and the rise of philanthropic funding), evidential practices (performance metrics and accountability requirements), and a humanitarian justification. Global health has become the usual term to describe this endeavour, which seeks to define health problems and set up interventions at a global scale. In order to study the scalability practices of global health, we propose to focus on a Geneva-based organization called GAVI. Created in 2000 by the World Health Organization, the World Bank, UNICEF, and the Bill and Melinda Gates foundation, the organization aimed to improve access to new vaccines in poor regions of the world (Roalkvam, *et al.*, 2013). With GAVI, money from wealthy governments and philanthropists is channelled towards the purchase of vaccines manufactured by private companies for the immunization programmes (the systematic vaccination of infants against a series of pathogens) of more than 70 countries with low GDP per capita.ⁱⁱ Here we will draw attention to one specific intervention managed by GAVI from 2010 onwards that was designed to scale up the use of second-generation pneumococcal vaccines preventing infections (otitis, pneumonia, meningitis and septicaemia) caused by the bacterium pneumococcus. This will allow us to explore in-depth the challenges of accomplishing scalability.

To account for scalability in global health interventions, we attend to a dual process: pivoting between referential work and forward projection. We suggest that referential work involves multiple efforts to produce evidential representatives that can stand as reference for matters on which an intervention is envisioned. Forward projection then involves the use of referential work as an evidential basis for projecting the intervention by anticipating its expansion and multiplying the delegates tasked with the job of making the envisioned change occur. As we shall see, this pivoting between referential work and forward projection helps establish a global health problem together with a suitable solution and provides the means to expand the solution and act on the problem. Global health interventions, we will suggest, rely on this alternation of an inward movement (referential work) and an outward movement (forward projection). Our analysis will be organized by following pneumococcal vaccines across different moments when this dual activity can be witnessed. We will show how through referential work and forward projection, disparate operations such as epidemiological research, advocacy, and market transactions are tied together to accomplish scalability.

Our analysis draws on fieldwork conducted in 2014-2016, including an extensive documentary review, 31 semi-structured interviews carried out mainly in Geneva and London and ethnographic observations of an epidemiological study in Burkina Faso (Spring 2015) and of a scientific conference in the UK (Summer 2016). Based on this empirical material, we will describe how the use of pneumococcal vaccines is probed and its future effect projected, how the value for money represented by making the vaccine widely available through aid spending is estimated, and how various frictions might unsettle the scaling up of vaccination against pneumococcus. But before turning to this analysis, we will begin with a consideration of scale.

On scale work

The emphasis on global evidence in this special issue provides an opportunity to unpack and reflect on scalability. Tsing's (2012) approach to scalability aims to denaturalise processes of expansion and remind us that 'making projects scalable takes a lot of work' (p. 507).ⁱⁱⁱ Global health, with its humanitarian focus on valuing all lives equally and alleviating human suffering (Lakoff, 2010),^{iv} calls for scaling up action to accommodate for this specific moral and evidential exigency. A global health intervention, such as routine immunization against pneumococcus in poor countries, is thus a useful example for examining the work through which scalability is accomplished. It offers a focal point for the arrangement of a variety of processes and evidential practices that make action at a (quasi) global scale possible.

One place to start thinking about scalability in relation to global evidence is with the aggregation capacity of statistical techniques. Already in Foucault's work on biopolitics (2007), mass vaccination is the epitome of governmental action, an intervention on a collective of individuals through the material environment they live with (their germs) made possible by a statistical mode of knowing. In Desrosières' terms (1998), statistics are particularly apt for making 'aggregates of things or people' (p. 67): they posit the existence of individual units (human beings), put them into relations of equivalence (age, sex, being alive or dead, sick or healthy, etc.) and open the possibility for large-scale entities, like populations, and phenomena, like mortality rates, to exist. The historical analysis by Wahlberg and Rose (2015) of the metric Disability-Adjusted Life Years (DALYs) pursues this line of enquiry around the articulation of statistical evidence and intervention. DALYs redefines diseases as something people live with, by accounting not only for mortality but also for negative impacts on everyday life. The technique quantifies the burden associated with diseases in order to better inform action and the allocation of resources. In particular, Wahlberg and Rose focus on the use of DALYs in the delineation of global health problems in need of a response of the same scale. They show that by describing the state of health across the world with DALYs and comparing the relative contribution of various diseases, the World Health Organization (WHO) prepared for scalable actions; the lack of attention paid so far to the high burden of mental disorders was made clear in the form of global evidence revealing a need for intervention.

The possibility offered by statistics to aggregate events is thus central to one aspect of scalability: bringing matters together in order that the size and importance of what emerge as shared characteristics can be acknowledged and acted on. But so too is the extrapolation capacity offered by statistics, when samples of people and things 'replace the whole by a part' so that it can be possible to 'return to the whole on the basis of one of its parts' (Desrosières, 1998, p. 211, 235). This movement across scale is what forms the basis on which new drugs and vaccines tested in a finite number of localized experiments (randomized controlled trials) are approved for routine use. This suggests that statistical evidence can enact a movement from the delineation of a

global health problem (making it recognizable) to the testing of a suitable solution to be expanded (making an intervention seem feasible).

The accomplishment of scalability through such a coupling of a large-scale problem and an expandable solution further requires what Cambrosio *et al.* (2006) have termed 'regulatory objectivity'. This type of objectivity is characterized by highly reflexive and geographically distributed modes of biomedical knowledge production and health intervention based on collectively agreed protocols, procedures and criteria (e.g. Keating and Cambrosio, 2003; Kholi-Laven, *et al.*, 2011). These help form standards that produce a shared understanding of diseases and comparable assessment methods.^v Their enactment is instrumental to scalability as it aims to ensure the replication of performance, either the performance of benchwork in laboratories or the performance of a treatment tested in clinical trials before being widely used (see Timmermans and Berg, 1997). Such processes of standardization also involve the creation of metrological representatives standing for broader wholes (referential microorganisms or trial subjects), which assumes a kind of biological universalism regarding what human bodies have in common. But this assumption on which scalability depends can turn out to be rather bold. Epstein (2009), for example, points to the overrepresentation in clinical experiments of adult white males compared to other types (gender, age, race). In a similar vein, Crane (2013) explains that most research on drug-resistant HIV uses as a reference the viral strain dominant in the United States which is not the most common strain in a place like Uganda. In both cases, findings based on these partial metrological representatives are generalized to much more diverse populations and settings. In other words, attending to standards reveals that scalability needs to establish a form of sameness that makes scalable action ill-suited to addressing diversity (Tsing, 2012).

Scaling up a health intervention, we will suggest, involves specific (and potentially questionable) evidential exigencies regarding disease rates, treatment efficacy, human bodies and germs, which are enmeshed with other considerations like political support and cost. Our description of how pneumococcal vaccines have been made widely available in poor countries seeks to capture the variety of settings and concerns that is attended to in global health. To accomplish scalability, a multitude of actors must then be enrolled, a point made particularly clear in Latour's (1983; 1993) study of how Pasteur developed the anthrax vaccine for animals.

Latour (1983) approaches scalability by putting the laboratory centre stage. It becomes the theatre of the proof through which the cause of anthrax (a microorganism) is isolated from the world of agriculture. The possibility that this isolation might lead to a viable solution to animal death is what recruits to the cause politicians, farmers, other scientists and writers from beyond the laboratory. But evidence of success requires an extension of the laboratory back into agriculture. This extension both enables the further enrolment of allies and the vaccination of thousands of cows and sheep that can stand among the corpses of the non-vaccinated. National bureaucracy and map-making also become involved, and other farmers are made aware of the problem and drawn to the solution, so that a decline in cattle's mortality rates across the French territory is eventually demonstrated. Although

isolating the germ might be regarded as small scale and national agriculture as large scale, Pasteur's intervention moves between these domains of action by deploying standard practices ('disinfection, cleanliness, conservation, inoculation gesture, timing and recording', *ibid.* p. 152) and mobilizing evidential techniques (laboratory tests and statistics, again).

Despite differences in time, place and size, child immunization against pneumococcus in poor countries also involves a single solution (vaccines) and a strong central coordination (through GAVI).^{vi} In order to understand how scalability works in global health, this paper will thus explore the scale work done by GAVI and its overseas aid donors, for whom, as we shall see, a key concern is the price of vaccines and the value for money represented by scaling up vaccination. Indeed, if we come back to Tsing (2012), scalability is closely related to the economic, the planning of production and the anticipation of return, a process of expansion that is both spatial and temporal.

To be used across the world, vaccines must be manufactured on a large scale, carefully packaged and delivered, but also desired and paid for by or on behalf of health administrations and their populations.^{vii} A focus on evidential practices such as cost-benefit ratios, which can balance a health effect with the spending required to obtain this effect, opens the possibility for thinking about the financial requirements of scalability. While pharmaceuticals are a (contested) source of income for companies,^{viii} they constitute an expense for those who purchase and use them. In this line of thinking, Sjögren and Helgesson (2007) examine how a Swedish health agency introduced cost-effectiveness analysis to select which drugs to subsidise with public money.^{ix} Again we see standardization in action (the determination of classes of products to be compared and common measures to assess health effects), now combined with market-oriented reasoning. In order to encourage a diversity of products and foster competition, Sjögren and Helgesson explain that the Agency decided to reimburse several producers within a price corridor and not only the most cost-effective drug. The purpose of such economic calculation conducted in the offices of a public administration is to act in return on patients, doctors and eventually on companies able to produce large amounts of pharmaceuticals.

To engage with scale and global evidence, then, is to open up questions of statistics, standards, laboratories, persuasive argumentation, costs and prices. We suggest that in global health interventions these questions take shape in a dual process of referential work and forward projection. This dual process is the focus for putting vaccines and evidence to work, and articulating epidemiological research, advocacy, and market transactions. Pivoting between reference and projection, we shall suggest, provides the basis for accomplishing scalability. But, as argued by Tsing (2012), 'scalability is never complete' (p. 510), and attention will also be paid to what escapes the expansionist project and causes friction along the way.

Accomplishing scalability

Probing through vaccines and projecting a global impact

In 2015, child immunization against pneumococcus was carried out in more than 50 poor countries with support from GAVI (GAVI, 2015b). Recommended by the WHO (2012), the use of pneumococcal vaccines in these regions began in 2010, only a few months after two pharmaceutical companies, GSK and Pfizer, had their pneumococcus vaccines licensed for use in Europe and the United States. While new vaccines tend to reach poor populations with a delay of at least 10 years (Greenwood, 2014), the rapid trajectory of scalability experienced by pneumococcal vaccines was accomplished through a series of moves, starting with efforts to draw together evidence of their efficacy and potential effectiveness if widely used.

To trace scale work related to pneumococcal vaccines, one place to start is the Gambia where in the 1980s initial evidence was gathered of the occurrence and seriousness of pneumococcal diseases in low income countries.^x This early work carried out by British epidemiologists showed that along with malaria and diarrhoea, bacterial pneumonia notably due to pneumococcus was a major cause of death among children. The pneumococcus bacterium lives in human noses and was first isolated in the mid-19th century. Hence its capacity to trigger infections has been known for some time. What was surprising to epidemiologists was the extent of the harm pneumococcus caused in the Gambia (interview 1), which called for further investigation. More studies were conducted from the mid-1990s that established the bacterial strains involved and revealed that the pneumococcal vaccine about to be licensed in the United States by Wyeth would only partially match this epidemiological profile (Adegbola, *et al.*, 2006).^{xi} Indeed, pneumococcus exists in more than 90 strains, and due to manufacturing constraints, only a limited number of strains can be targeted by a single vaccine (Bogaert, *et al.*, 2004). Wyeth's product eventually licensed in 2000 targeted the seven strains mainly responsible for pneumococcal diseases in the American population, while evidence from the Gambia, as well as other African locations like Malawi, indicated that the commercially available vaccine would not suit these settings (Gordon, *et al.* 2003).

As a first generation vaccine was put to use in the United States, research continued in order to develop a product with broader epidemiological coverage. Key to building evidence of and confidence in the likely success of a modified pneumococcal vaccine was a trial carried out in the Gambia in the early 2000s. The tested vaccine was an *ad hoc* product provided by Wyeth, combining the seven-valent commercial vaccine with two additional antigens against strains that had been singled out in epidemiological surveys conducted in African countries (these two antigens were eventually included in the second generation vaccines in use since 2010). By hosting the vaccine trial, the Gambia as 'the tropics in miniature' (Kelly, 2015, p. 306) operated as a referential resource. Pneumococcal vaccine here could act as a probe for generating evidence of its likely future effects, while the research site was called upon to stand in as reference for Africa and the trial to stand in as representative of pneumococcal vaccination in other but similar locations.

The Gambian trial was an experiment in the sense that it deployed a metrological infrastructure to contain and detect the effect of injecting new molecules into people's bodies. Altogether 17,000 children were randomly assigned to two groups, one

receiving the vaccine and the other a placebo, and, after vaccination, every case of pneumonia was counted for several years (Cutts, *et al.*, 2005). ‘It was a big difficult trial’ from the point of view of the investigation team (interview 1). Many challenges had to be dealt with, such as flooded buildings, transportation delays, constant risks of sample contamination and the overloading of the IT system by the amount of data produced. Experimenters struggled to get the Gambian ‘resource-poor settings’ to comply with ‘good clinical practices’ meant to ensure the quality of results (Cutts, *et al.*, 2006, p. 1). These difficulties needed to be overcome, but also acted as a reference point: they stood in for the difficulties likely to be faced across the resource poor settings into which the vaccine might be launched.

To achieve a certain status as an adequate representation through which scalability might be accomplished, the trial ought to fit the standards of what Cambrosio *et al.* (2006) have termed ‘regulatory objectivity’. The Gambian experiment belonged to a loosely coordinated network of trials, implemented around the same period in South Africa, the United States and the Philippines, all testing the performance of pneumococcal vaccines against pneumonia. To increase comparability between these trials, the WHO (2001) had standardized the diagnosis technique, how chest radiographs should be interpreted to recognize bacterial pneumonia. This established a common definition of what ought to be measured and what ought to count as a desirable effect when assessing vaccination against pneumococcus. The vaccines used in the network of trials were not strictly speaking identical but prototypes manufactured by a few different companies (Wyeth but also Sanofi for example). The interconnected experiments aimed to show that vaccination against a certain number of pneumococcal strains, beyond the 7 included in the only commercialized product, could work in distinct locations. As one of the trial investigators affirmed (interview 1), these locations included ‘poor rural Africa’ for which the Gambia was considered ‘typical’.

In a clinical trial, randomisation and subsequent statistical analysis are meant to ensure that the tested product (here pneumococcal vaccines) rather than other factors can be assigned a measured performance so that scaling up the intervention would induce repetition of the performance. The different pneumococcal trials produced consistent results (O’Brien, *et al.*, 2009), but the assumed typicality of the Gambia further increased the capacity of this particular experiment to speak for the future effect of pneumococcal vaccines in low income settings. When its results became public, the Gambian trial acquired an even greater status as analysis showed that in the vaccinated group, the mortality rate was 16% lower than in the control group (Cutts, *et al.*, 2005). The number was significant and unexpected. It had been assumed that the experiment would detect pneumonia cases with good statistical power. But the significant reduction in mortality became the evidence ‘to which actually most of the attention was dedicated’, explains a statistician involved in the trial design (interview 2). The Gambian vaccine trial was called a ‘vaccine probe’, simultaneously and straightforwardly proving that pneumococcus killed children and that vaccination could prevent those deaths. Although many more clinical trials and myriad testing (for safety) were required for second generation pneumococcal vaccines manufactured by Pfizer (which had bought Wyeth) and GSK to be licensed in 2010, this initial

referential work was crucial because it demonstrated that with the right antigens the problem of pneumococcus could be effectively addressed in what was construed as poor rural Africa.

Accomplishing scalability depended on two-fold referential work: first the deaths recorded in the trial could stand in as reference for a more general cause of death (pneumococcus as problem), and then the efficacy rate of the vaccine could stand in for future prevention of death (vaccine as solution). Referential work meant problem and solution could be brought together on the same page. After drawing things in (cause of death, ability to prevent death, trials and tests), the next step was to then project things out. In particular, the extent of future effects was explicitly anticipated and made public. This pivot between drawing in and projecting out seems characteristic of scalability. In the case of pneumococcal vaccines, central to this projection was a policy-oriented, evidence-gathering initiative called PneumoADIP. A few years into its existence, GAVI, the new aid organization specialized in buying vaccines, had started considering forthcoming vaccines that could be added to national immunization programmes. Pneumonia caused by pneumococcus had been identified as a major cause of infantile death in a WHO-related epidemiological assessment (Bryce, *et al.*, 2005), and in 2004, GAVI launched PneumoADIP to better document the need for and advantages of future second generation pneumococcal vaccines in low income countries (Levine, *et al.*, 2004). Led by epidemiologists at Johns Hopkins University, the project practised a form of what Storeng and Béhague (2014) call ‘evidence-based advocacy’. Grants for pneumococcal disease surveillance were provided to research teams to improve the evidence base (Knoll, *et al.*, 2009) and meetings were organized in Africa and Asia to assemble the health policy community of these regions (interview 3). PneumoADIP’s objective was to bring the problem of pneumococcus outside the small world of epidemiologists.

To accomplish scalability, to move from reference to projection, involved an assessment of the extent of the public health problem represented by pneumococcal diseases. The scale of the problem could then be used to underpin the potential scale of the solution. In the late 2000s, the PneumoADIP team collaborated with the WHO to collect, review, and combine epidemiological data published from studies conducted across the world in order to estimate the ‘global disease burden’ of pneumococcus. The meta-analysis quantified the number of deaths and episodes of disease (pneumonia, meningitis, and other invasive diseases) caused by the bacterium. To ensure a valid outcome, statistical evidence from as many places as possible was needed. Yet, many hypotheses and assumptions are necessarily involved in this kind of modelling exercise wherein extrapolation is the norm (see Wendland, 2016). The objective is not to have an accurate count of every disease case and death, an impossible task at this scale, but a reliable enough indication of the size of the problem. Results from the four vaccine trials evoked above (in the Gambia, United States, South Africa and the Philippines) provided key information to the assessment. They helped quantify the percentage of pneumonia cases (the main pneumococcal disease) attributable to the bacterium rather than other pathogenic agents like viruses. Modellers eventually computed that in 2000 about 800,000 children under five years old were dying worldwide because of pneumococcus (O’Brien, *et al.*, 2009). The

number represented a large burden mostly located in Sub-Saharan Africa and South Asia.

Through further modelling, epidemiologists could then project the impact of carrying out immunization in all countries eligible for GAVI's help. To obtain such a global impact, modellers built on the unexpected outcome of the Gambian trial. The burden of pneumococcus and the 16% efficacy rate against mortality were put side by side and the result adjusted using other data (average immunization coverage, global demographic trends). The capacity to save many children's lives, 262,000 annually to be precise, was thus assigned to the widespread use of suitable pneumococcal vaccines (Sinha, *et al.*, 2007). Published in the influential journal *the Lancet*, the number of lives saved was meant to 'pull on your heartstrings', acknowledged a member of PneumoADIP (interview 4). In conference rooms, policy papers and Power Point slides, research outcomes were translated into the language of what McCoy *et al.* have termed the 'emotive metric of "lives saved"' (2013, p. 5).^{xii} The quantified and probabilistic effect of a prototype vaccine was used to project a future health impact achievable through a large-scale intervention (making pneumococcal vaccines available to poor populations). This move from localised clinical research to recruitment to the pneumococcal cause was productive, even if it created unease. It is said that epidemiologists who participated in the Gambian trial experienced blunt advocacy based on cautious results as a 'bit crude' (interview 5), while partaking in the consensus among pneumococcus experts that PneumoADIP could be praised for having raised awareness around pneumococcal diseases and vaccination.

Pivoting between reference work and projection enabled pneumococcal vaccines to become associated with a positive humanitarian purpose: enacting the principle that all children's lives are of equal worth and thus all worthy of being saved (see Lakoff, 2010). Advocacy and global epidemiological projection based on referential results generated from the Gambian trial accomplished scalability. This achievement depended on demonstrating the size of the problem (the burden of disease) together with the size of the impact if the problem was addressed (with vaccination), in order to enrol support to make this global expectation a reality. When second generation pneumococcal vaccines became available, national governments eagerly applied to GAVI Secretariat, giving the new vaccine one of the quickest uptake rates in the short history of the organization. PneumoADIP was successful in making the case for vaccination to health administrations but also, as we will see now, to overseas aid donors.

Cost estimates and value for money ratios

Evidence collected and generated by PneumoADIP could present pneumococcus as a high-gain low-risk spending option for overseas aid; low risk because second generation vaccines more suitable to the epidemiological settings in which GAVI intervened were about to be licensed, and high gain because many lives ought to be saved through immunization. These characteristics of pneumococcal vaccines were particularly appealing to a group of donors that in the mid-2000s was ready to finance

a pilot Advance Market Commitment (AMC). The pilot AMC aimed to accelerate access to new vaccines for poor populations through a conditional and subsidized purchase guarantee. Bringing into being this intervention managed by GAVI, required further scale work pivoting between reference and projection around notions of cost and return.

The idea of an AMC originated around 2000 in the work of an academic economist (Kremer, 2000). It was proposed as a market solution to the neglected health problems of poor countries and their people, which from this economic vantage point suffer from a lack of purchasing power. In an AMC, if a biomedical innovation like a new vaccine is developed that proves able to address a neglected health problem, it would be purchased under specific conditions for the benefit of the affected population.^{xiii} The attraction of an AMC for vaccines took hold in overseas aid policy-making in the mid-2000s. It became a publicised diplomatic matter at G7 finance summits and five governments (the UK, Italy, Norway, Canada and Russia) together with the Gates Foundation eventually pledged 1.5 billion dollars to an AMC for pneumococcal vaccines whose terms were negotiated between 2007 and 2009 (Dalberg, 2013; McGoey, 2014). By drawing on the existence of near-commercial products, the evidentiary work of PneumoADIP and its humanitarian advocacy, finance ministers thought they could quickly scale up immunization against pneumococcus in poor countries and claim that many lives would be saved (interviews 7, 10). The AMC was thus established as a conditional purchase guarantee, fixing in place and for a long time (a minimum of 10 years) a unique price for pneumococcal vaccines bought by GAVI, and disbursing the 1.5 billion dollar pool of money as an additional subsidy. The objective of the contractual offer was to encourage investment by pharmaceutical firms in production capacity for the new vaccine (more and bigger manufacturing plants) to meet the now solvent demand.

In order for pneumococcal vaccines to be subsidized via the AMC, purchased by GAVI through the conditional offer and routinely used by health administrations, price had to occupy a key position around which referential work could be arranged and given purpose. One focus for pricing was pharmaceutical firms: what kind of price structure would encourage them to increase production and supply pneumococcal vaccines to poor countries? For about two years, civil servants, economists (including the inventor of the AMC concept), and vaccine manufacturing experts interacted at a distance with each other to set the contractual offer.

The pricing structure of the AMC was discussed through economic reasoning (GAVI, 2008; Snyder, *et al.*, 2011). Business valuation practices were simulated to try and work out ‘from the perspective of the manufacturers, what kind of investments may be justified under different programme structures’, recalls an economist (interview 6). Drawing a world of financial reference into this contractual structure was challenging. Companies are usually wary of releasing commercially sensitive data and empirical insights to feed the model were scarce, making the pricing exercise necessarily ‘arbitrary’ as suggested by McGoey (2014, p. 120). To balance this informational asymmetry, help came from the PneumoADIP project that had tasked a consultant with enquiring into the business of pneumococcal vaccines, meet with patent holders

and estimate production costs. For the vaccine to be able to induce protection in children against a given strain of pneumococcus, the manufacturing process requires binding the correspondent antigen to a protein. This requirement, which makes the vaccine difficult to produce at an industrial scale (and limits the coverage of targeted strains), was widely acknowledged as the major cost determinant. The pricing guesswork conducted by the consultants eventually quantified a cost of about 2 dollars a dose. The number was then used as what Caliskan (2010) terms a 'prosthetic price', an input into the calculation of an actual price.

After lengthy debate informed by simulations that assessed different price and subsidy ranges, the group in charge of the pricing design eventually settled on a contract offer of 3.5-dollars a dose, with a 3.5-dollar subsidy disbursed as a per-dose top-up in the early years of supply to help firms cover their investment cost, up to a total amount dependent on supplied volumes (Cernuschi, *et al.*, 2011)^{xiv}. The offer was conditional; the purchase would be honoured and the subsidy transferred only if health administrations requested pneumococcal vaccines from GAVI. As with other vaccines, GAVI Secretariat would then interact with the UNICEF supply division in Copenhagen to ensure the shipment of doses from plants in Ireland, Belgium or Singapore, to African international airports, and then along the cold chain to healthcare centres. The AMC thus established a unique price for the market represented by the 73 countries supported by GAVI, enabling a further pivot in scalability. This referential work drawing the pharmaceutical industry into the intervention could support a forward projection: a potential volume of more than 200 million vaccine doses to be put into circulation annually.

This uncertain referential work, which assembled what could be made from commercial evidence and the presumed requirements of pharmaceutical firms, was not the only focus for the pricing arrangement. Donors who provided the money also had to be worked on. Senior politicians like Gordon Brown, then UK Chancellor of the Exchequer, had been central to the decision to commit their government to funding the AMC, with the UK contributing almost one third of the 1.5 billion dollar pool (interview 7). But for diplomatic commitment to translate into flows of currency and market transactions with vaccine manufacturers, the AMC had to be presentable as a form of public spending that would generate a return of substantial value. Another kind of evidential activity was thus required that can be seen in paperwork from the British Department for International Development (DFID). There, referential work around price was accomplished through the standard metrological device of Disability Adjusted Life Years (DALYs) and a ratio, the cost per DALYs averted. These metrics could further act as a pivot, from drawing in financial matters to projecting out health impact.

In value for money ratios utilising DALYs and vaccine prices as a basis for assessment, elements of the Gambian vaccine probe can still be traced, buried in the parameters used to quantify a future health impact balanced against its cost (Snyder, *et al.* 2011). The metric of DALYs captures the range of negative effects of diseases, from minor disability to early death (see Wahlberg and Rose, 2014), but in the estimate of DALYs caused by pneumococcal diseases in poor countries, disability did

not count for much. DFID used the composite measure (instead of mortality) less for its calculative sophistication than for its status as an evidential standard. The relevant indicator was then the cost per DALY averted, whose numerical value depended on the pricing design of the AMC (the lower the price and subsidy for pneumococcal vaccines, the higher the number of purchased doses for a fixed UK contribution, the higher the number of healthy life years saved). The World Bank had established a 100-dollar benchmark under which the cost per DALY averted was said to be excellent value for money. The ‘business case’, a mandatory procedure to spend public money in the UK, could refer to this standard of overseas aid and, according to a British civil servant, the final contractual terms of the AMC came out as being ‘good enough’ value for money (interview 7). Cost estimates and DALYs thus enabled a forward projection once again; that vaccine doses ought to be funded and delivered, and lives hopefully saved.

Political support from a finance minister and administrative authorisations were necessary to ensure the full deployment of the intervention, but were still insufficient to accomplish scalability. Shifting from a concern for evidence of value for money to a projection back out into the practical processes through which immunization could take place, also required navigation of GAVI’s funding procedures. Although the AMC subsidized the purchase of pneumococcal vaccines, its funds would not cover the main vaccine price set in the contractual offer (3.5 dollars a dose). This cost fell to GAVI’s budget, also made of overseas aid money raised during replenishment events and provided by governmental and philanthropic donors through multi-year pledges. Introducing pneumococcal vaccines in immunization programmes on a large scale and in a reliable manner over many years involved ensuring the future of GAVI whose capacity to pool funding and collect requests for vaccines made it central to the accomplishment of scalability.

For GAVI, pneumococcal vaccines were just one product of its vaccine portfolio. The vaccine portfolio, which has a familiar financial sound, was used to manage GAVI’s investments in global health in a similar manner to what Doganova and Muniesa (2015) call a ‘capitalization device’. By drawing distinct market transactions and interventions together in one place, the vaccine portfolio enacted a referential sensibility. GAVI Secretariat has been using the device to assess how vaccines perform in relation to each other according to a series of indicators (impact on child mortality, number of producers, price etc.). For products not yet purchased, it could inform programmatic decisions, suggesting priorities between diseases. For products already bought by GAVI, it could guide further adjustment. A few years into the use of pneumococcal vaccines in an increasing number of countries, one indicator stood out: relative cost, or ‘the cost of the health impact that you are buying’, explains a member of GAVI Secretariat (interview 8). Relative cost was expressed as another value for money ratio between vaccine cost for GAVI (mainly its price multiplied by volumes requested by health administrations) and health impact estimated by epidemiological modelling (Lee, *et al.*, 2013). The indicator singled out pneumococcal vaccines as the most expensive product of the portfolio and this evidence encouraged GAVI Secretariat to actively and successfully negotiate with

GSK and Pfizer a slight price reduction below the 3.5 dollar cap offered in the AMC (GAVI, 2015, p. 11).

Relative cost echoes the economic performance of cost per DALYs averted used by British overseas aid to justify its spending on the AMC. The vaccine portfolio could thus also provide a pivot between referential work and forward projection. It allowed GAVI to continuously check on the value for money represented by pneumococcal vaccines and further intervene in the market transactions ensuring the daily circulation of vaccine doses. Such a scalar device enables what Latour would term a ‘mobilization of the [vaccine] world’ (1987, p. 225) in a highly localized site, GAVI’s Geneva offices. The organization could put different vaccines (considered as assets whose return is a health impact) into competition so that its own performance as an investor in global health could improve. However, this mobilization of the vaccine world achieved by GAVI is an on-going process that can become a matter of friction. As we will go on to note now, scale work also raises questions and uncertainties, indicating that its terms need to be continually revisited.

Friction, questions and a changing bacterium

Of course, moving from referential work to forward projection in order to accomplish scalability does not operate instantly and smoothly. In GAVI’s office, ensuring that vaccination against pneumococcus can take place involved demand forecasts, application procedures, shipment oversight, and bank transfers. Logistics are not without challenge and vaccine shortages, overloaded nurses, malfunctioning equipment, difficulties for parents in accessing healthcare centres or refusal to see their children vaccinated, produce myriad frictions in countries supported by GAVI (Roalkvam, *et al.*, 2013, field notes). Expansion without change might remain out of reach (cf. Tsing, 2012) and logistics is not the only source of trouble in child immunization against pneumococcus. Other kinds of friction (pricing issues and bacterial adaptation) can also be noted. They highlight that continual attention must be paid to referential work and forward projection in order to practically, and always partially, accomplish scalability. In place of expansion without change, with friction comes a continuing attentiveness to the possibility of change.

The first friction examined here concerns financial matters. In making expenditure transparent, the AMC triggered public concerns over its pricing structure. Médecins Sans Frontières (MSF), speaking on behalf of the ‘taxpayers’, criticized the AMC as a ‘scandalously expensive’ subsidy scheme (MSF, 2011). It even urged readers of British newspapers to ‘keep in mind the \$19bn made by the two companies – UK-based GSK and Pfizer – solely on sales of a vaccine that protects children against pneumonia, a condition that kills 1 million children every year’ (Elder, 2015). MSF picked corporate revenues available in annual financial reports as the relevant metric to gauge vaccine prices. Selling at more than 130 dollars in the US (Rosenthal, 2014), pneumococcal vaccine is for Pfizer a ‘blockbuster’ that justified the acquisition of Wyeth (interview 9). In light of such huge profits, for MSF the 3.5 dollars per dose of the AMC (a child is usually considered immunized after 3 doses) was already too

high and the subsidy unjustifiable. MSF sought to unsettle the legitimacy of the intervention and incite donors not to be content with the current terms of transaction (see also MSF, 2015). By invoking a number that appeals to humanitarian ethics, the death of one million children a year, MSF did not contest the need for pneumococcal vaccines, nor the scale of its use. Quite to the contrary, it asserted that greater scalability could be achieved by changing the referential criteria used in setting prices

Such complaints by MSF about the AMC terms sought to put pressure on GAVI and donors to revisit scale work around price. It notably revealed that questions regarding the future ability of health administrations to purchase vaccines without GAVI's support had been marginalized. These questions have only become a concern for GAVI Secretariat recently as a few countries' GDPs started moving out of the low-income threshold of eligibility (interview 10). A vaccine price that may seem justifiable on the terms on which donors usually forecast spending might not be sustainable for a health administration's strained budgets in lower income settings. This suggests that what counts as the reference of a beneficial outcome always depends on normative assumptions. Scalability as it has been enacted through the evidential practices examined so far – especially value for money ratios – tended to make overseas aid a necessity for the implementation of child immunization against pneumococcus. That is, it remained unclear to what extent or to what scale, health administrations could justify and pay for the vaccine price set in the AMC without donor contributions.

If logistical problems and publicly articulated concerns with vaccine prices provide bases for friction in accomplishing scale, another friction arises through continual epidemiological monitoring of pneumococcus. What is at issue here is the pivoting between referential work and forward projection based on which efficacy rates of pneumococcal vaccines obtained in clinical trials were used to anticipate a global impact and to advocate for vaccination (along with calculating vaccine prices and a return on public aid spent to cover the cost). Once vaccines started to be routinely administered in countries supported by GAVI, it became possible to attend to the actual epidemiological consequences of the intervention. GAVI Secretariat provided grants to the research community for a dozen impact studies (GAVI, 2015). In such places as the most inhabited city in Malawi, on the Kenyan coast, in the south-west of Burkina Faso or in rural Gambia these studies were tasked with assessing the effectiveness of pneumococcal vaccines.

A central question for these impact studies concerned pneumococcal strains in circulation in people's noses that still caused disease even under routine immunization. This question mattered to epidemiologists and other scientists like geneticists who expected that the scaling up of vaccines might transform the bacterial species (Weinberger, *et al.*, 2011). Once molecules manufactured in a standardized way are introduced in children's bodies, scalability in the sense proposed by Tsing (2012, p. 507) of being kept 'self-contained, unable to make relationship[s]', cannot be guaranteed. The 10 or 13 pneumococcal strains targeted by the two vaccines purchased by GAVI would tend to disappear, but could be replaced by other strains and clones likely to cause infection. This phenomenon of replacement had been

witnessed in the United States following the introduction of first generation products against 7 strains. Besides evidence that the latter vaccine would not match the epidemiological profiles of poor regions with a high disease burden, bacterial replacement was an important motivation for a second generation vaccine. This dynamic of replacement has not led experts to question the usefulness of vaccination, because the new pneumococcal population that established itself in American people's noses seemed much less harmful and maybe even useful to keep at bay more dangerous germs from human microbial flora. However, with vaccines being used at a quasi-global scale and in more diverse epidemiological settings, pneumococcus's capacity to adapt called for careful scrutiny.

Bacterial replacement could not have appeared during temporary trials, nor was its anticipation integrated in projecting the future effect of vaccination. Impact studies were tasked to monitor the consequences of this scale work and it was within such consequences that the phenomenon was made witness-able. The circulation and transformation of bacteria across and inside human bodies formed another kind of movement through scale uncontrolled by GAVI (unlike the delivery of vaccination). The purpose of *ex post* surveillance was to register this movement in the form of transmission and infection patterns.

The impact studies all carried out similar clinical, laboratory, and statistical analyses, but each assessment remained localized in the sense that there was no attempt to collate their results into broader evidence of vaccine effectiveness. Debates among specialists at an international conference on pneumococcus in 2016 revolved precisely around the difficulties of generalizing from the patchy set of investigations (field notes). Preliminary results were puzzling as they showed very different effects depending on the people and bacteria investigated. The studies from the Gambia and Malawi suggested vaccination had only a moderate positive impact on disease rates and some strains targeted by the vaccine persisted, while research in Kenya detected a very high impact. What could explain the discrepancy? Could it be due to differences in climate, in people's general health (HIV, malnutrition, etc.), in living conditions, in the logistics of child immunization or in the manufactured molecules (Kenya was using GSK's vaccine, the two other countries Pfizer's)? Providing answers to these questions has only begun. What is already clear here is that scalability ran into issues with the differentiated consequences of vaccination that distinct impact studies brought to light. It was not possible to assign with confidence to a study a referential status and generalize local findings to produce a statement about a global effect.

'We have been too complacent' stated an epidemiologist during his keynote to imply that the enthusiasm, with which his peers had welcomed second-generation vaccines and the mobilization of resources through the AMC and GAVI, should now be nuanced by on-going epidemiological interrogation paying more attention to diversity (field notes). This critical attitude towards the accomplishment of scalability contrasts with how GAVI described the effects of its actions to donors and the general public. In 2015, an 'outcome evaluation' of the AMC was conducted by consultants and claimed that pneumococcal vaccines had prevented about 250,000 early deaths since 2009 (BCG, 2015, p. 58). The number derived from modelling, according to

calculations similar to those of PneumoADIP, including efficacy rates from trials carried out with vaccine prototypes back in the early 2000s, but now adjusted with actual uptakes (volume of doses requested by countries from GAVI and bought via the AMC). Though the size of this outcome was lower than anticipated when the vaccine was still a matter of advocacy, it was promoted as a sign of success for the AMC and GAVI.

Scale work must incessantly deal with different sorts of friction, from logistical troubles to controversy over prices and the capacity of bacteria to adapt. If the number of children's lives saved attributed to the AMC and its management by GAVI seemed to provide satisfactory evidence of success to donors, it could not convince epidemiologists busy quantifying localized changes in disease rates and in the distribution of pneumococcal strains. Continuous epidemiological work aimed to question and unsettle the accomplishment of scalability. Unsettling the accomplishment of scalability can be seen as a pragmatic way to remind participants in the intervention of the purpose of the endeavour (improving health across the world). This careful scrutiny could make diversity together with the challenge it poses to scale work witness-able and prepare for the scaling up of another, maybe more differentiated action (perhaps third generation pneumococcal vaccines), thus opening up new cycles of referential work and forward projection.

Conclusion

This paper aimed to explore the kind of evidential exigencies involved in making action at a global scale possible. To do so, we examined how child immunization against the pneumococcus bacterium was scaled up in low income countries, from early epidemiological findings, to the mobilization of overseas aid to purchase the vaccine through an organization called GAVI, and the ongoing questioning of the financial terms and epidemiological effects of the intervention. Our focus was on the practical accomplishment of scalability and the possibilities of expanding without change.

The global health intervention we have described did rely on a kind of global evidence, evidence of the worldwide burden of diseases attributed to pneumococcus obtained from the collation of local epidemiological data and some modelling. But the paper also showed that the intervention involved myriad other evidential practices, and that these practices were closely associated with the enrolment of political support through advocacy techniques, the set-up of contractual terms, in particular prices, to buy vaccines from manufacturers, the justification of spending public money on overseas aid, the logistics of cold chains and the scientific understanding of diseases and pathogens. This implies that to be translated into scalable action with transformative effect, evidential activity in global health interventions must be considered in relation to political, administrative, and market activities.

To analyse the accomplishment of scalability, we traced the pivoting between referential work and forward projection that seemed to characterize how

pneumococcal vaccines have become widely used in low income countries. We thus attended to a clinical trial carried out with vaccine prototypes in a typical rural African setting, the Gambia. We showed that the trial results could stand as a reference for the future effect of vaccination in poor countries, and this piece of evidence was indeed used in epidemiological modelling to anticipate a global impact and advocate for the use of the vaccine. We then moved to discussions around the set-up of an Advance Market Commitment to subsidize the purchase of pneumococcal vaccines so that companies manufacturing the product would be encouraged to scale up their production capacity. We looked at the devices through which estimates of manufacturing costs and the calculation of different value for money ratios were used by GAVI and its donors as references to establish the pricing structure and buy large volumes of vaccines. Finally, we paid attention to the frictions of scaling up, beyond the expected logistical troubles of bringing vaccine doses to remote healthcare centres. Here we foregrounded further debate about vaccine prices in light of health administrations' strained budgets before focusing on the continual scrutiny exercised by epidemiologists cautious about claiming success.

This last point indicated a tension inherent to scale work: when a single intervention (in our case in global health) is expanded, the broad entities (people and germs) which are intervened on are likely to react in unexpected and diverse ways, indicating that further intervention better attuned to these differences is needed. For Tsing (2012), with whom we introduced the paper, it seems that scale work is problematic and doomed to fail because it ignores or erases the diversity of our world. Valuing diversity to critically engage with attempts to scale up is in her case a normative stance. Through our exploration of a global health intervention, we would like to propose a more nuanced conclusion regarding scalability as an empirical process with moral consequences. Child immunization is the governmental action *par excellence*, whose normative aim is to provide health on a large scale, ideally to the greatest number of people across the world. There is a sort of authoritative equalitarian drive in such an endeavour that does not easily accommodate for diversity. The intervention we have described and its use of partial epidemiological data and broad categories (poor rural Africa) is rather insensitive in this respect (cf. Neyland *et al.*, 2017). But, at the same time, the paper showed that its relative insensitivity translated into a transformative action (vaccines have been brought to many African countries) that revealed diversity. Evidence that people and bacteria living in distinct and distant places across the African continent react differently to the vaccine is an outcome of scaling up the intervention. Diversity appears against the assumption of sameness and comparability; it is made witness-able through scalability. To us, this suggests that scalability is a focal point for managing and reducing evidential exigencies in global action, but also that pivoting between referential work and forward projection to accomplish scalability can become the means through which new exigencies appear. In place of expansion without change comes expansion always alert to the possibilities of change.

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ⁱ Overseas aid refers here to the transfer of technical and financial resources from high income to low income countries.

ⁱⁱ After vaccination lost momentum within overseas aid in the 1990s, the creation of GAVI put vaccine centre-stage again, notably by more actively engaging with the pharmaceutical industry (Roalkvam, *et al.*, 2013). In 2017, GAVI pooled funding from 20 donors, bought 11 different types of vaccine, and fulfilled demand from 73 countries (including grants for improving immunization systems). See: <http://www.gavi.org/>.

ⁱⁱⁱ We can see this at work in efforts to reform health care systems, where large scale interventions overlook local differences and local innovations face problems in accomplishing scale (Bloom and Ainsworth, 2010).

^{iv} Alongside ‘humanitarian biomedicine’, Lakoff (2010) identifies a second ‘regime of global health’: ‘global health security’. The latter refers to emergency arrangements deployed to detect and intervene on new pathogens able to rapidly spread across the world in an age of intensified global circulations (on flu viruses, see Lakoff 2015). While for pathogens like Ebola, vaccination responds to what is considered a security threat, in the case of a commensal bacterium like pneumococcus, the security focus seems less prevalent.

^v In the case of antidepressant drugs, McGoey (2010) reveals a lack of consensus about the diagnosis method and debate about whether the standard experimental design of RCTs is the proper method to assess these treatments.

^{vi} The case provides a striking contrast to the programme against malaria vectors in Dar es Salaam described by Kelly and Lezaun (2014), for which the idiosyncrasies of the city, its stagnant waters and the local administration become the focus of a set of mundane and *ad hoc* actions.

^{vii} In the case of insect-as-food, Yates-Doerr (2015) shows that the scaling up of such an intervention against global hunger is challenged by the difficulty of packaging the new market good (insects) for long distance travel and the different tastes of consumers.

^{viii} Pharmaceutical prices are controversial (see Light and Warburton 2011), partly because costs are not made public while access to the products can be a matter of life and death.

^{ix} Further building on the ‘market devices’ literature (Callon, *et al.* 2007), Maldonado Castaneda (2017) examines the evidential tools (including cost-effectiveness analysis) used by pharmaceutical companies in setting and justifying the price of HPV vaccines.

^x Although it is now financed by GAVI, the practical implementation of child immunization is still very much a state-run, national intervention; hence the pervasive use, by the actors and ourselves, of countries’ name to refer to the geographical location of epidemiological work.

^{xi} Due to the development of antimicrobial resistance in the 1970s, vaccines has become for epidemiologists the best means to intervene on pneumococcal diseases. As infants tend to carry more bacteria and be more vulnerable, child immunization ought to effectively reduce the circulation of the pathogen and prevent infection in the whole population (Bogaert, *et al.*, 2004).

^{xii} The focus on children and the morally charged assessment of the number of lives saved also aim to enroll the donor community whose spending are critical to GAVI's existence.

^{xiii} From the start, vaccines were to be the focus of an AMC given the presumed cost-effectiveness of such a technology; a single action providing long-term protection.

^{xiv} The amount of subsidy received in a supply agreement is calculated as follows: the annual volume of doses offered by the manufacturers is compared to an indicative demand target of 200 million doses annually, the percentage of the target demand covered by the offered supply then matches the percentage of the 1.5 billion dollar subsidy fund received for that offer, and the volume of doses for which the 3.5 dollar top up is added to the 3.5 dollar price is calculated accordingly.

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