The promise and challenges of nanovaccines and the question of global equity

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Among the many potential benefits arising from the rapidly advancing field of nanomedicine is the possibility of a whole new range of nanovaccines in which novel delivery mechanisms utilizing nanoparticles could make obsolete the use of needles for administering any vaccine. However, as the massive resources of the worldwide pharmaceutical industry are deployed to develop nanovaccines, urgent questions arise as to which diseases should be targeted and which populations will benefit most. This paper explores how such targeting of nanovaccines might be decided in an ethically optimal way and considers some of the practical considerations and potential problems of implementing such a global nanovaccine policy. There seems little doubt that nanomedical research could develop vaccines against most major global infectious diseases. Throughout the history of medicine, however, it is well recognized that insufficient attention and resources have been given to public health and preventive medicine and the environmental causes of ill-health remain under-researched. We urge that national governments and regional authorities of wealthier countries incentivize their powerful pharmaceutical corporations to develop nanovaccines within a global and long term perspective and not just to focus on the diseases of the developed world.

Keywords: adjuvant, developing countries, equity, global health, nanomedicine, nanotechnology, nanotoxicology, nanovaccine, preventive medicine, resource allocation ethics

Nanoscale medical applications, known as nanomedicine, are now developing rapidly (Tibbals, 2010). Despite the wide array of difficulties to be overcome in designing and manufacturing novel medicines and vaccines on the scale of 1 to 100 nanometres (1 nm = 1 millionth of a millimetre), already there is a rapid and global growth of research and development activities, publications and conferences in this field. The global market in nanomedicine was valued at

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$72.8 billion[1] in 2011 and is predicted to reach $130.9 billion by 2016 (Fisher, 2012). Among the many possibilities of "nanopharm" is that of nanovaccines: novel vaccines that are based on the techniques and materials of nanotechnology. This should immediately raise the questions of 'nanovaccines' for what conditions and for which populations? The earlier the questions are asked the better, since priorities are already being set and targets selected.

It may be thought that the term 'nanovaccine' is just a semantic change, because existing vaccines (e.g., those based on viruses) are already in the nanoscale. However, here 'nano' refers (for example) to innovative delivery vehicles and methods, such as micelles or liposomes, deliberately designed in the nanoscale using new techniques and materials. The widely publicized Australian Nanopatch delivery system, which promises to make the use of needles for vaccinations a thing of the past, is likely to be first of many such new nanosystems (Raphael et al., 2010).

Equity

Looking at global patterns of morbidity and mortality for infectious disease, the ethical question of equity is raised. If nanovaccines are to be developed by deploying massive resources, both financial and human, which diseases are to be targeted and which populations will benefit most? Inequity is already apparent where standard vaccines are concerned, and it is not yet clear whether things are improving, particularly when the "four leading causes of young child mortality in the developing world, including lower respiratory infections (pneumonias and bronchiolitis), infectious diarrhoea, malaria and measles, are in part preventable by immunization with existing vaccines or vaccines that are currently in development" (Levine et al., 2009, p. 275). Whether these rates will improve with the development of new vaccines seems uncertain, given that simple vaccines for some of the most preventable diseases are not already available to those who might need them most. For instance:

> It is also believed that a notable proportion of all severe pediatric diarrheal disease in developing countries is caused by a few pathogens including rotavirus, Shigella and enterotoxigenic *Escherichia coli*, for which vaccines either exist (rotavirus) or are at an advanced stage of development (Shigella and enterotoxigenic *E. coli*). Some major causes of adult death in the developing world, such as cervical cancer and hepatocellular cancer, are also preventable with existing vaccines (human papillomavirus and hepatitis B virus (HBV) vaccines, respectively) (Levine et al., 2009, p. 276).

From a humanitarian point of view, questions about equity need to be asked earlier, rather than later, and particularly about the growth of the nanomedicine project because, being new, it offers an unprecedented opportunity to correct omissions and deficiencies made in the past. Once this project has developed in a particular direction, the invested effort and resources will tend to engender their own rationale and impetus, regardless of questions of ethical priority.

Ethical issues arising from the topic of healthcare resource allocation are not new, of course. Added to standard problems is the ongoing uncertainty (and even unease) about how we understand and apply terms like 'equity'. It is not the role of this paper to engage with these debates in detail; nevertheless, a short introduction to the issues is appropriate. For instance,

[1] US dollars and billions (10^9) are used in this paper.

though there tends to be a *general* consensus that "health inequity constitutes inequalities in health that are unfair or unjust" (Mitchell et al., 2009), such claims are not without controversy. One problem is that what people will understand as *fair* or *unfair, just* or *unjust* may not be easily agreed upon. It might seem *unfair* that an individual's likelihood of good health may be at least partly determined by where they are born, or where they grow up, but this does not necessitate that such differences are also *unjust* (though of course they may well be). In attempting a definition of equity, and other related terms, Kawachi et al. (2002) note that "additional considerations such as whether the inequalities are avoidable or unnecessary" raise further difficulties. This can, for instance, apply when we try to adopt "preventability and necessity as criteria for the definition of health inequity". Since inequity and equity are "political concepts, expressing a moral commitment to social justice" (Kawachi et al., 2002), these terms remain just as slippery as the terms 'moral commitment' and 'social justice' themselves.

> The crux of the distinction between equality and equity is that the identification of health inequities entails normative judgment premised upon: (a) one's theories of justice; (b) one's theories of society; and (c) one's reasoning underlying the genesis of health inequalities. Because identifying health inequities involves normative judgment, science alone cannot determine which inequalities are also inequitable, nor what proportion of an observed inequality is unjust or unfair (Kawachi et al., 2002).

Disagreement in such areas can hinge on issues about free will, autonomy and choice. Yet, despite such uncertainties, these debates are perhaps less controversial when discussing equity on a global scale. For instance, it would be fair to say that the possibilities for choice and autonomy are in fact greatly diminished where the potential for decision-making is restricted to those countries with more wealth, power or capacity for research, innovation and development. It would also be fair to say that this scenario is not at all far from the present global reality.

How decisions are made about resource allocation and who contributes to those processes can be rather opaque. As Guerrier (2012, p. 256) points out, equity of *access* to resources is just one area for concern; transparency in the rationality of decisions is just as important. With influenza vaccines, for example, the World Health Organization (WHO) currently plays the role of vaccine 'distributor', and relies on its own systems of evaluation and expertise. The "criteria, principles and guidelines" by which vaccines are distributed are thus "not the result of a global process to work out this policy, involving all actors in the international community". In addition, the "ethical foundations of these criteria are not entirely explicit", regardless of whether such criteria are fair or not, which of course they may well be (Guerrier, 2012, p. 261). Drawing attention to this is not to detract from the value of the work being done by the WHO. Instead, it is to make the point that the *credibility* and *effectiveness* of vaccine distribution (Guerrier, 2012, p. 262) could be improved by greater transparency in the decision-making process.

This model can be applied to the issue of increasing equity, where transparency of decision-making processes, as well as greater involvement of stakeholders in communication about nanovaccines, will be important steps towards improving *how* resources are accessed on a global scale. This includes transparency for decisions made on a local scale. Resources allocated for the poorer can sometimes be in danger of being siphoned off to benefit those who are wealthier, since those with more wealth are more likely to be involved in the distribution of resources. As Victora et al. note, "even when interventions are equitably targeted, rich people

take advantage of them more rapidly than do poor people, so that inequity ratios could widen initially when a new effective intervention becomes available" (2003, p. 237).

'Universal coverage approaches' can be problematic for these reasons. Yet targeting resources can engender other problems, including the danger of stigmatization (Victora et al., 2003, p. 238). It is clear that neither approach offers a catch-all solution and both must be evaluated in context. Understanding context is therefore crucial, and to do so effectively requires both communication and education. By communication we mean *discussion*, as emphasised by Mitchell et al. (2009). This may involve stakeholder engagement, and would require context-specific cultural understanding. Associated issues of trust cannot be over-emphasized. For instance, "the conditions under which a society accepts the usefulness of a vaccine are so complex that a vaccine can be perceived at one moment as a useless danger, and at another as an indispensable product" (Guerrier, 2012, p. 258). Reciprocal communication is therefore important, but given the likelihood of failure in effective communication even within a culture with which one is familiar (as exemplified by the crisis of confidence with the MMR vaccine in the UK in the late 1990s (Deer, 2011)), the likelihood of failure across cultures seems only more likely. This is particularly so where communication is mostly information dissemination. Equity requires that there is also parity in the communication process, such that all stakeholders (whether at the trial stage of a medicine or later in its development or distribution) are able to engage in a discussion about risk and benefit on a level playing field (or as level as it can possibly be, given specific contexts).

Standard risk/benefit analyses with regard to nanomedicine, which would include environmental and health impacts, may also need to be widened to include contextually specific ethical questions:

> There are also potential risk management issues specific to developing countries: displacement of traditional markets; the imposition of foreign values; the fear that technological advances will be extraneous to development needs; and the lack of resources to establish, monitor, and enforce safety regulations (Singer et al., 2005, p. 63).

Other factors to consider include how people engage with health workers and whether basic needs are being met in other areas, including access to fresh water, food, fuel, and adequate accommodation. Where these and other basic needs are not being met, it may be that vaccination, by comparison, is not seen as a priority. Also, if a family can afford the medicine to successfully treat an illness once it happens, seeking out the vaccination against such illness may not be seen as a priority (Mitchell et al., 2009). The fact that the infected person could then infect others, some of whom may not be able to afford treatment themselves, also needs to be a factor in the decision-making processes for distribution, especially where contracting an illness may be associated with social stigmas in certain cultures.

Ensuring resources are available is not the same issue as accessibility. Enabling people to access those resources is far more complex, and involves a more subtle understanding of context and culture. To address these challenges effectively, as we note above, will also "require active participation on the part of developing countries" (Singer et al., 2005, p. 63), such that discussion is key. It is clear that preventing inequity cannot be a simple matter of providing resources universally, without also taking into account how these services are understood and accessed by local people. This also includes the cost of travel and time away from work, homes and families (Mitchell et al., 2009).

Despite some of the difficulties in solving the practical difficulties of achieving equity in resource allocation, it is clear that to do so must remain a priority:

> The great number of child deaths due to easily preventable diseases, and the huge mortality reductions that might be expected to arise if inequities were eliminated, suggest that the lifesaving potential of improving equity is far greater than that of any new technology or combination of technologies that could be introduced in the future (Victora et al., 2003, p. 240).

Embedded in the general question of whether nanomedicine will continue to perpetuate or even accentuate inequity by creating a 'nano-divide' (Royal Society, 2004, pp. 52–53), including in healthcare (Baumgartner, 2008, pp. 76–77) are two specific ethical questions concerning those conditions amenable to vaccine research and development. Firstly, can and will nanovaccine developers and manufacturers address those neglected conditions that globally have the highest morbidity and mortality, such as dengue, leishmaniasis, schistosomiasis, trypanosomiasis, trachoma and onchocerciasis (river blindness) (Hotez et al., 2009, p. 1570)? Secondly, can and will they prioritize the development of research into protection against the growing risk of pandemics, especially from new strains of viruses, such as A/H5N1, which recent research suggests may only require four or five mutations for mammal-to-mammal species transmission (Russell, 2012, pp. 1541–7)? As far back as 2000, a WHO report inferred that through the convergence of ever-expanding globalized travel and climate change (Githeko et al., 2000), infectious diseases, even those usually thought of as 'third world' problems, can extend their usual zone of incidence rapidly and extensively. This means that the ethical question of new vaccines for the underprivileged today could tomorrow easily become the broader question of vaccines for the human race as a whole.

There is already some evidence that nanotechnology in industry, manufacturing, defence, transport, food and agriculture, communications, and consumer goods will widen the gap between 'developed' and 'developing' nations (Mehta, 2002, p. 273). However it has also been argued that the efficiencies of nanotechnology could enable the latter to leapfrog some economic developmental stages and catch up (Appelbaum et al., 2011). The same questions of justice and inclusiveness arise for nanovaccines, but in a particularly pressing way, since it is the current and future health of the human race that is at stake. Evidence for global equity in the field of medicines generally is not encouraging. It has been estimated that of 1233 new drugs that reached the global market in 1975–1997, only 13 were applicable to the tropical conditions causing the most infectious disease deaths (Pirages, 2005, p. 46). Meanwhile, one should consider that outside the drug development arena, nanotechnology generally could lead to public health benefits; for example, creating novel means of detecting pathogens and contaminants in air–soil–water, nanofiltration and remediation of water supplies (Theron et al., 2008), and indirect effects such as those accruing from enhanced waste management (Kassim, 2005, pp. 209–10).

Nanomedical priorities

The United States' National Institutes of Health *Roadmap for Medical Research in Nanomedicine* defines nanomedicine as "an offshoot of nanotechnology, (which) refers to highly specific medical interventions at the molecular scale for curing disease or repairing

damaged tissues, such as bone, muscle, or nerve"(National Institutes of Health, 2006). Such a definition is a powerful indicator that we are witnessing too high a priority being attached to a curative approach within nanomedicine, and even then this is principally directed at diseases such as cancer and Parkinson's disease, which are of prime concern in the developed world, where the greatest purchasing power is located. This is further reflected in the fact that nano-oncology, nanocardiology and even nano-ophthalmology are now recognized subspecialties of nanomedicine (Wong and Liu, 2012, p. 943) and there is even an already well established journal devoted to nanoneurology (Sharma, 2009).

Throughout the history of medicine, however, it is well recognized that insufficient attention and resources have been given to public health and preventive medicine, and the environmental causes of ill-health remain under-researched. For example, at least 216 man-made chemicals in the environment are known to induce breast cancer in mammals (Rudel et al., 2007), yet many of these have as yet not been researched in relation to breast cancer in women (Brody et al., 2007), although there is evidence (for example) for a link with breast cancer and exposure to polycyclic aromatic hydrocarbons (PAHs) (Brody et al., 2007, pp. 2693–7). Sources of exposure to PAHs include exhausts of Otto and Diesel engines, as well as smoking. Comparatively little emphasis is given to such concerns in terms of medical and healthcare development; such exposure has always tended to be treated as a marginal 'environmental health' matter. Unfortunately, the same primacy of curative medicine and, especially, a focus on nanopharmaceuticals (Barwarski, 2008) has already developed within nanomedicine.

There is little doubt that, within the ambit of public health and preventive medicine, nanomedical research could develop vaccines against major global infectious diseases. Take the case of novel adjuvants. An adjuvant is an agent that enhances the immune response to co-inoculated antigens in a vaccine without having any specific antigenic effect itself (Aguilar and Rodriguez, 2007, p. 54), the word being derived from *adjuvare*, the Latin for 'to help' or 'to enhance' (Vogel, 1998, p. 241). There are relatively few adjuvants used in existing vaccines and the need for both new delivery systems and immune potentiators remains high (Peek, 2008, p. 919). A novel calcium phosphate nanotechnology adjuvant for new vaccines (Peek, 2008, p. 915) (including military biodefence vaccines for toxins such as anthrax and ricin) and drug delivery systems was developed as far back as 2000 (He et al., 2000; He et al., 2002).

More could be done, but only if the ethical and political will is present. Worldwide, it is estimated that two thousand million people (i.e., about one in three people) have been infected with hepatitis B and, of those, 350 million people remain chronically infected and, consequently, are at greatly increased risk of liver cancer (Colvin and Mitchell, 2010); there are around 600,000 deaths every year from HBV-related liver disease, especially in Africa, Asia and Latin America (WHO, 2012).

The first plasma-derived HBV vaccine was licensed in the USA in 1981 (WHO, 2012). This was replaced in 1986 by a recombinant version expressing the hepatitis B surface antigen. Two single-antigen vaccines are currently available—Engerix B and Recombivax HB—but neither is ideally suited to conditions in many developing countries. They both require refrigeration between 2 and 8 °C for storage and maximum immunity requires the administration of three doses over a prolonged period of time—the first two doses a month apart and the third one six months after the second dose (Mast and Ward, 2008). The requirement for syringes and

needles for the administration of each dose also introduces further potentially avoidable hazards, considering it is estimated that 21 million new hepatitis B infections annually are due to unsafe injections in healthcare settings (Hauri et al., 2004).

A nano-emulsion is a new delivery method for antigens already used for existing hepatitis B vaccines and which obviates the use of needles. The University of Michigan's Nanotechnology Institute for Medicine & Biological Sciences has developed such a needleless method of vaccination, based on a superfine emulsion of oil, water and surfactants administered intranasally (Makidon et al., 2010) (the research was supported by the Grand Challenges in Global Health Initiative (2005)).

Potential benefits

The reason that ethical questions arise about the prioritization of nanovaccine research and development is that such vaccines hold out the promise of therapeutic benefits over existing vaccines and even a reconceptualization of the entire approach to vaccine design and vaccination methods.

One major benefit of a nanotechnological approach to vaccine design is that attention can more easily be given to the molecular design of the delivery vehicle, targeting the nanovehicles to particular microorganisms or cells through molecular recognition and also ensuring an optimally timed release. Nanovaccines can be designed for a balanced delivery appropriate to the disease condition (i.e., an optimal biodistribution of the vaccine). It should be possible to design the size, shape and surface of the delivery vehicle to achieve the desired distribution.

Many traditional vaccines contain potentially unsafe or controversial adjuvants, hence researchers continue to look for alternative adjuvants (Stanberry and Strugnell, 2011, pp. 153–7), such as squalene, which is used in cytomegalovirus (CMV) vaccines currently in development (Stanberry and Strugnell, 2011, p. 155). Nanotechnology may be able to provide better alternatives; for example, by making the adjuvant more directly recognizable to the immune system. Traditional adjuvants such as aluminium, present (for example) in human papillomavirus (HPV) vaccines (Stanberry and Strugnell, 2011, p. 155), are often used without a theoretical understanding of how they actually work, whereas with better control at the nanoscale what is often a shortcoming may be overcome. This would mean perhaps reducing the number of less promising adjuvants (experimentally there are hundreds) and using a much smaller dose of adjuvant.

A nanotechnological approach may also circumvent the possible hazards of vaccine preservatives. The use of a form of mercury as a preservative has been controversial for some time. Thiomersal is an organomercury compound in use for about 70 years to prevent pathogenic contamination of vaccines. In higher doses than are found in vaccines, thiomersal has been associated with both nephrotoxicity and neurotoxicity (Pfab et al., 1996). However, the current consensus is that there is no hard evidence for such toxic effects at the much lower levels used in vaccines (Clements, 2004). Nevertheless, both the European Agency for the Evaluation of Medicinal Products (EMEA, 2001) and the WHO (2000) have instructed vaccine manufacturers to remove thiomersal from vaccines as a precautionary measure. It has already been shown that such removal of thiomersal has had no detrimental effect on the efficacy of the influenza vaccines AGRIPPAL and FLUAD and "the range of frequencies, severities, and durations of each local and each systemic reaction was lower than that expected from previous

clinical trial data" (Toneoatto, 2004, p. 460). Theoretically it seems to be possible, through greater control at the nanoscale, to design effective nanovaccines that do not involve the addition of any hazardous substances.

Potential risks

At the same time as the realization of these possible advantages, it has to be recognized that nanovaccines may introduce new uncertainties about toxicity and other new hazards of their own, which would have to be addressed along with the development of the nanovaccine, influencing their design and testing. Indeed, nanotoxicology and nanomedicine should be regarded as two sides of the same coin and should ideally be developed together (Linkov et al., 2008). Special attention should be paid to specific forms of toxicity such as immunotoxicity and genotoxicity (Asha Rani et al., 2009), and issues such as bioaccumulation (the biological sequestering of a substance at a higher concentration than that at which it occurs in the surrounding environment) and biodegradability (Hagens et al., 2007). Biopersistence (Hoet et al., 2004) may be a two-edged sword since a vaccine does need to continue working for a long period before booster administrations are required, but persistent side effects would not be acceptable.

Nanoparticle adjuvants for vaccines need to be designed to optimize vaccine absorption and immunogenicity but then biodegrade as soon as possible after they have served their purpose. For example, whilst having similar properties to aluminium salts, calcium phosphate-based adjuvants are less biopersistent and have low, if any, toxicity, being "a natural compound to the human body" (Petrovsky and Aguilar, 2004). Researchers at Duke University in the USA have synthesized a nanoparticle adjuvant that has been shown to not only enhance immunity in mice at the site of administration but also to be capable of travelling to the lymph nodes where it acts on many cell types of the immune system to generate a greatly increased immune response (St John et al., 2012).

The immune system itself, of course, works at the nanoscale, so therapeutic enhancement often runs dangerously close to unwanted toxicity; many nanoparticles are picked up quickly by phagocytes, which may or may not be what the nanovaccine designer wants, depending on the specific condition being vaccinated against. However, inadvertent recognition of nanoparticles as foreign will trigger an autoimmune response against them, leading to toxic effects and even death (Zolnik et al., 2010). It is, however, possible to shield nanoparticles from unwanted immune recognition by (for example) attaching polymers such as polyethylene glycol to them (Moghimi 2002). Nanoparticles also interact with other important immune mechanisms such as the complement system, activation of which by nanoparticles could be harmful, for example at tumour sites, where complement activation is known to stimulate tumour progression (Moghimi and Andresen, 2009). By contrast, at an intradermal or subcutaneous vaccination site, complement activation could enhance vaccine effectiveness (Reddy et al., 2007).

A new theoretical approach?

Nanoscale manipulation and design may provide an opportunity for a novel vaccine approach aimed at producing a (more or less) generic nanoscale platform to which diverse molecules

could be attached, depending on the condition and therapy proposed. In a sense, a nanomaterial could be designed like a Swiss Army knife, the parts of which could be added, removed, activated or deactivated depending on the intended medical purpose. The engineered surface of a micelle, for example, could work in this multifunctional way. Such an approach could create greater therapeutic flexibility and efficiency, also reducing manufacturing costs and the need to create and test new adjuvants for every new vaccine. Advanced computer modelling could facilitate the prediction and control of therapeutic and toxic effects. A first step would be the interdisciplinary and cooperative effort and openness to generate the extensive data needed for such a stochastic process. Emergent properties at different levels of complexity (subcellular, cellular, tissue, organ, etc.) could be managed within such an approach.

Also on the horizon, but controversial, is the possibility of DNA vaccines, and this might also converge with nanotechnological concepts and methods. In the DNA vaccine model, the vaccine comprises a plasmid containing a stretch of DNA that encodes for the antigen against which immunity is desired. The antigen is produced *in situ* by the DNA and is recognized as a foreign element to be destroyed. Despite the theoretically anticipated advantages of such a vaccine, until very recently the situation does not appear to have changed very much from 2005, when Donnelly et al. reported that "the disappointing potency of the DNA vaccines in humans underscores the challenges encountered in the efforts to translate efficacy in preclinical models into clinical realities." However Kong (2012) has now demonstrated complete immunity from influenza in mice by using a recombinant attenuated bacterium. He considers that the innovative technique could be applied to the rapid manufacture of effective vaccines against virtually any infection at dramatically reduced cost and without risk to either those vaccinated or the wider public. If this hope is eventually confirmed, the method may overtake alternative previous suggestions that the effectiveness of DNA vaccines might be transformed by means of nano-engineered targeting vehicles. Saade and Petrovsky (2012) nevertheless consider that polymer nanoparticles (Xiang et al., 2010) continue to show promise as DNA vaccine adjuvants.

Vaccines for developing countries

The research and development necessary for nanovaccines are likely to be considerable, even if in the long term there would be efficiencies and savings. Developing countries may find the more sophisticated techniques to be well out of their financial reach. Since we can no longer assume that highly infectious diseases will remain localized, it may be considered a matter of urgency for the national governments and regional authorities of wealthier countries to incentivize their powerful pharmaceutical corporations to develop nanovaccines within a global and long term perspective.

There are obstacles to be overcome. The ethical imperative demands that vaccines be approached in a different way, even on the technical level. For example, the poor heat stability of new vaccines would have to be countered for use in regions of high ambient heat and poor or absent refrigeration. Vaccines ought increasingly to be manufactured in the country of use. There is, however, a danger in developing vaccines solely for developing countries. There is a question of trust and perception here: it might appear to the public that 'they are testing vaccines on us'. One should be wary of 'Western' judgments being imposed on developing countries, and ideally the healthcare workers and patients of those countries should be making their own judgments and decisions. What is needed is a renewed global strategy

based on open stakeholder dialogue involving national governments from both sides of the nano-divide, together with regional and international organizations, healthcare professionals, patients' organizations, pharmaceutical corporations and SMEs fulfilling a multitude of adjunct operations.

Acknowledgments

This paper is the development of a poster presentation and multidisciplinary discussion at a conference organized by the EU FP7 coordinating project NanoImpactNet (NMP4-CA-2008-218539, Grant Agreement 218539), in which St Mary's University College was a funded partner. The conference was held in Lausanne, 14–17 February 2011, and the authors are grateful to all participants for their contributions.

References

Appelbaum, R.P., Parker, R., Cao, C. (2011). Developmental state and innovation: nanotechnology in China. *Global Networks* 11, 298–314.

Asha Rani, P.V., Mun, G.L.K., Hande, M.P., Valiyaveettil, S. (2009). Cytotoxicity and genotoxicity of silver nanoparticles in human cells. *ACS Nano* 3, 279–290.

Barwarski, W.E., Chidlowsky, E., Bharali, D.J., Mousa, S.A. (2008). Emerging nanopharmaceuticals *Nanomedicine.* 4, 273–282.

Baumgartner, C. (2008) Bionanotechnology: a new challenge for ethical reflection? In: *Emerging Conceptual Ethical and Policy Issues in Bionanotechnology* (ed. F. Jotterand), pp. 67–84. Dordrecht: Springer.

Bharali, D.J., Mousa, S.A., Thanawala, Y. (2007). Micro- and nanoparticle-based vaccines for hepatitis B. *Adv. Exp. Med. Biol.* 601, 415–421.

Brody, J.G., Moysich, K.P., Humblet, O., Attfield, K.R., Beehler, G.P., Rudel, R.A. (2007). Environmental pollutants and breast cancer: epidemiologic studies. *Cancer* 109 (Suppl. 12), 2667–2712.

Clements, J. (2004). The evidence for the safety of thiomersal in newborn and infant vaccines. *Vaccine* 22, 1854–1861.

Deer, B. (2011). How the case against the MMR vaccine was fixed. *BMJ* 341, c5347.

Donnelly, J.J., Wahren, B., Liu, M.A. (2005). DNA Vaccines: progress and challenges. *J. Immunol.* 175, 633–639.

EMEA (2001). *Points to Consider on the Reduction, Elimination or Substitution of Thiomersal in Vaccines* (document CPMP/BWP/2517/00).

Fisher, M. (2012) *Global Nanomedicine Market to Reach $130.9 Billion by 2016* https://connect.innovateuk.org/web/nanopharm/articles/-/blogs/6547458;jsessionid=059847980CFB4FAFF1755C7AC33EFC83.oav1ovMo (accessed 30/11/2012).

Githeko, A., Lindsay, S.W., Confalonieri, U.E., Patz, J.A. (2000). *Climate Change and Vector-Borne Diseases: a Regional Analysis*. Geneva: WHO (http://www.scielosp.org/pdf/bwho/v78n9/v78n9a09.pdf; accessed 3/1/2013).

Grand Challenges in Healthcare Initiative (2005). http://www.grandchallenges.org/Pages/GCGHGrantsAwarded.aspx?TDate=all&ProjectID=213 (accessed 3/1/2013).

Guerrier, M. (2012). Comment: ethics and epidemics: reflections on contemporary stakes in transparency and equity. In: *Influenza and Public Health: Learning from Past Pandemics* (eds. J. Gunn, T. Giles-Vernick, S. Craddock), pp. 256–265. London: Routledge.

Hagens, W.I., (2007). What do we (need to) know about the kinetic properties of nanoparticles in the body? *Regulatory Toxicol. Pharmacol.* 49, 217–229.

Hauri, A.M., Armstrong, G.L., Hutin, Y.J. (2004). The global burden of disease attributable to contaminated injections given in health care settings. *Int. J. STD AIDS* 15, 7–16.

He, Q., Mitchell, A., Morcol, T., Bell, S.J.D. (2002). Calcium phosphate nanoparticles induce mucosal immunity and protection against herpes simplex virus type 2. *Clin. Diagn. Lab. Immunol*. 9, 1021–1024.

He, Q., Mitchell, A.R., Johnson, S.L., Wagner-Bartak, C, Morcol, T., Bell, S.J.D. (2000). Calcium phosphate nanoparticle adjuvant. *Clin. Diagn. Lab. Immunol*. 7, 899–903.

Hoet, P.H.M., Brüske-Hohlfeld, I., Salata, O.V. (2004). Nanoparticles—known and unknown health risks. *J. Nanobiotechnol.* 2, 12.

Hotez, P.J., Fenwick, A., Savioli, L., Molyneux, D.H. (2009). Rescuing the bottom billion by control of neglected tropical diseases. *Lancet* 373, 1570–1575.

Hunt, G. (2008). Negotiating global priorities for technologies. *J. Industrial Ecol.* 12, 275–277.

Hunt, G. (2006). The Global ethics of nanotechnology In: *Nanotechnology: Risk, Ethics & Law* (eds G. Hunt, M. Mehta), Ch. 15. London: Earthscan.

Stratton, K.R., Howe, C.J., Johnston, R.B.J. (eds) (1994). *Adverse Events Associated with Childhood Vaccines: Evidence bearing on causality*. Washington, DC: National Academy Press.

Kassim, T.A. (2005) Waste minimization and molecular nanotechnology: toward total environmental sustainability. *Handbook Environmental Chem.* 3, 191–229.

Kawachi, I., Subramanian, S.V., Almeida-Filho, N. (2002). A glossary for health inequalities. *J. Epidemiol Community Health* 56, 647–652.

Kong,W., Brovold, M., Koeneman, B.A., Clarke-Curtiss, J., Curtiss, R. (2012). Turning self-destructing *Salmonella* into a universal DNA vaccine delivery platform. *Proc. Natl Acad. Sci. USA* 109, 19414–19419.

Levine, M.M., Robins-Browne, R. (2009). Vaccines, global health and social equity. *Immunol. Cell Biol.* 87, 274–278.

Linkov, I., Satterstrom, F.K., Corey, L.M. (2008). Nanotoxicology and nanomedicine: making hard decisions. *Nanomedicine* 4, 167–171.

Makidon, P.E., Nigavekar, S.S., Bielinska, A.U., Mank, N., Shetty, A.M., Suman, J., Knowlton, J., Myc A., Rook, T., Baker, J.R., Jr. (2010). Characterization of stability and nasal delivery systems for immunization with nanoemulsion-based vaccines. *J. Aerosol Medicine Pulmonary Drug Delivery* 23, 77–89.

Mast, E.E., Ward, J.W. (2008). Hepatitis B vaccines. In: *Vaccines*, 5th edn (eds S.A. Plotkin, W.A. Orenstein, P.A. Offit. Elsevier Health Sciences).

Mehta, M. (2002). Nanoscience and nanotechnology: assessing the nature of innovation in these fields. *Bull. Sci. Technol. Society* 22, 269–273.

Mitchell, S., Andersson, N., Ansari, N.M., Omer, K., Soberanis, J.L., Cockcroft, A. (2009). Equity and vaccine uptake: a cross-sectional study of measles vaccination in Lasbela District, Pakistan. *BMC International Health and Human Rights* 9 (Suppl. 1), S7 (accessed 28/1/2013).

Moghimi, S.M. (2002). Chemical camouflage of nanospheres with a poorly reactive surface: towards development of stealth and target-specific nanocarriers. *Biochim. Biophys. Acta* 1590, 131–139.

Moghimi, S.M., Andresen, T.L. (2009). Complement-mediated tumour growth: implications for cancer nanotechnology and nanomedicines. *Mol. Immunol.* 46, 1571–1572.

Nandedkar, T.D. (2009). Nanovaccines: recent developments in vaccination. *J. Biosciences* 34, 995–1003.

National Institutes of Health (2006). *National Institute of Health Roadmap for Medical Research: Nanomedicine* (http://nihroadmap.nih.gov/nanomedicine/; accessed 3/1/2012).

Peek, L.J., Middaugh, C.R., Berkland, C. (2008). Nanotechnology in vaccine delivery. *Advanced Drug Delivery Reviews* 60, 915–928.

Petrovsky, N., Aquilar, J.C. (2004). Vaccine adjuvants: current state and future trends. *Immunol. Cell Biol.* 82, 488–496.

Pfab, R., Muckter, H., Roider, G., Zilker, T. (1996). Clinical course of severe poisoning with thiomersal. *Clin. Toxicol.* 34, 453–460.

Pirages, D. (2005). Containing infectious diseases. In: *WorldWatch Institute State of the World 2005*. New York: W.W. Norton.

Raphael, A.P., Prow, T.W., Crichton, M.L., Chen, X., Fernando, G.J., Kendall, M.A. (2010). Targeted, needle-free vaccinations in skin using multilayered, densely-packed dissolving microprojection arrays. *Small* 6, 1785–1793.

Reddy, S.T., van der Vlies, A.J., Simeoni, E., Angeli, V., Randolph, G.J., O'Neil, C.P., Lee L.K., Swartz, M.A., Hubbell, J.A. (2007). Exploiting lymphatic transport and complement activation in nanoparticle vaccines. *Nature Biotechnol.* 25, 1159–1164.

Royal Society (2004). *Nanoscience and nanotechnologies:opportunities and uncertainties* (http://royalsociety.org/uploadedFiles/Royal_Society_Content/policy/publications/2004/9693.pdf; accessed 3/1/13).

Rudel, R., Attfield, K.R., Schifano, J., Brody, J.G. (2007). Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer research. *Cancer* 109 (Suppl. 12), 2635–2667.

Russell, C.A., Fonville, J.M., Brown, A.E.X., Burke, D.F., Smith, D.L., James, S.L., Herfst, S., van Boheemen, S., Linster, M., Schrauwen, E.J., Katzelnick, L., Mosterín, A., Kuiken, T., Maher, E., Neumann, G., Osterhaus, A.D.M.E., Kawaoka, Y., Fouchier, R.A.M., Smith, D.J. (2012). The potential for respiratory droplet–transmissible A/H5N1 influenza virus to evolve in a mammalian host. *Science* 336, 1541–1547.

Saade, F., Petrovsky, N. (2012). Technologies for enhanced efficacy of DNA vaccines. *Expert Rev. Vaccines* 11, 189–209.

St John, A.L., Chan, C.Y., Staats, H.F., Leong, K.W., Abraham, S.N. (2012). Synthetic mast-cell granules as adjuvants to promote and polarize immunity in lymph nodes. *Nature Materials* 11, 250–257.

Shan, S., Poinern, E., Ellis, T., Fenwick, S., Le, X., Edwards, J., Jiang, Z.-T. (2010). Development of a nanovaccine against wild bird H6N2 avian influenza virus. *Procedia in Vaccinology* 2, 40–43.

Singer, P., Salamanca-Buentello, F., Daar, A. (2005). Harnessing nanotechnology to improve global equity. *Issues Sci. Technol.* 21, 57–64.

Sharma, H.S. (2009). Nanoneuroscience is an established discipline now. *J. Nanoneurosci.* 1, 95–96.

Stanberry, L.R., Strugnell, R. (2011). Vaccines of the future. *Perspectives Vaccinology* 1, 151–199.

Theron, J., Walker, J.A., Cloete, T.E. (2008). Nanotechnology and water treatment: applications and emerging opportunities. *Critical Rev. Microbiol.* 34, 43–69.

Tibbals, H.F. (2010). *Medical Nanotechnology and Nanomedicine.* Boca Raton: CRC Press.

Toneatto, D., Bugarini, R., Corbellini, B., Penlington, M., Vaccina, D., Minutello, A. (2004). Thiomersal removal: effects on the safety and immunogenicity of the Chiron influenza vaccines AGRIPPAL® and FLUAD®. *International Congress Series* 1263, 457–460.

WHO (2000). Thiomersal as a vaccine preservative. *Weekly Epidemiological Record* 2, 12–16.

WHO (2012). Hepatitis B fact sheet (http://www.who.int/mediacentre/factsheets/fs204/en; accessed 3/1/2013).

Victora, C.G., Wagstaff, A., Schellenberg, J.A., Gwatkin, D., Claeson, M., Habicht, J.P. (2003). Applying an equity lens to child health and mortality: more of the same is not enough. *Lancet* 362, 233–241.

Vogel, F.R. (1998). Adjuvants in Perspective. In: *Modulation of the Immune Response to Vaccine Antigens* (eds F. Brown, L.R. Haaheim). Vol. 92, pp. 241–248. Basel: Karger.

Wong, K.K.Y., Liu, X.L. (2012). Nanomedicine: a primer for surgeons. *Paediatric Surgery International* 28, 943–951.

Xiang, S.D., Selomulya, C., Ho, J., Apostolopoulos, V., Plebanski, M. (2010). Delivery of DNA vaccines: an overview on the use of biodegradable polymeric and magnetic nanoparticles. *Wiley Interdisciplinary Rev. Nanomed. Nanobiotechnol.* 2, 205–218.

Zolnik, B.S., González-Fernández, A., Sadrieh, N., Dobrolovskaia, M. (2010). Nanoparticles and the immune system. *Endocrinology* 151, 458–465.