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Social values and scientific evidence: the case of the HPV vaccines

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Abstract Several have argued that the aims of scientific research are not always independent of social and ethical values. Yet this is often assumed only to have implications for decisions about what is studied, or which research projects are funded, and not for methodological decisions or standards of evidence. Using the case of the recently developed HPV vaccines, we argue that the social aims of research can also play important roles in justifying decisions about (1) how research problems are defined in drug development, (2) evidentiary standards used in testing drug "success", and (3) clinical trial methodology. As a result, attending to the social aims at stake in particular research contexts will produce more rational methodological decisions as well as more socially relevant science.

Keywords HPV vaccine · Values in science · Evidence for use

Introduction

There is growing consensus that the aims of science often depend on social aims (Kitcher 2001; Solomon 2001; Longino 2002; Kourany 2003). Kitcher has argued that the main goal of science is not merely to discover truths about the world, but particularly *significant* truths, which are determined by human values and interests (Kitcher 2001, 44). Yet some assume that this only has implications for which research programs to pursue or prioritize and does not affect scientific methodology or standards of evidence. For example, Kitcher (2001) focuses only on how to democratize decisions about research priorities. Similarly, Solomon (2001) is

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concerned with promoting a fairer distribution of research resources and effort among empirically adequate research programs that are driven by different values and interests. This assumption reinforces the position that values may play a legitimate role in the context of discovery, but not in the context of justification.

We argue that when the aims of research depend on social values, such values not only have implications for research priorities but also help justify methodological decisions and standards of evidence. Using the case of the recently developed human papillomavirus (HPV) vaccines, we show that social, as well as epistemic, aims of the research play an important role in methodological decision-making during basic research and in the design and execution of clinical trials. In examining the development of HPV vaccines, we show that the justification for a variety of methodological and evidentiary decisions depends partly on the extent to which they promote the social aims of the research. In the final section, we draw out the normative implications this has for research practices.

The case of the HPV vaccine

HPV, estimated to be the most common sexually transmitted infection worldwide, affects approximately 20 million people in the United States and 6.2 million are newly infected each year (Dunne and Markowitz 2006). Worldwide, genital HPV infection affects 440 million people (WHO 2008).

There are over 100 HPV types, which are classified as "high-risk" and "low-risk" according to the likelihood of developing cancer after infection (WHO 2008). Although in most cases HPV infection is transient, persistent infection with high-risk HPV types is the major cause of cervical intraepithelial neoplasia (CIN) and cervical cancer (Bosch et al. 2002). The most common high-risk HPV types are 16, 18, 45 and 31, with HPV 16 and 18 accounting for about 70% of all genital cancers (WHO 2008).

Cervical cancer is the second most common cancer among women worldwide. Nearly 500,000 women are diagnosed with it each year, and over 250,000 die of the disease (WHO 2008; Parkin et al. 2005). 83% of these cancers occur in developing countries, with Latin America, sub-Saharan Africa, and South and Southeast Asia having the highest incidence (Parkin et al. 2005). In the US, in 2004, genital HPV infection resulted in nearly 12,000 new cases of cervical cancer and 3,850 women died from the disease (U.S. Cancer Statistics Working Group 2007).

Two prophylactic vaccines, Gardasil® and Cervarix®, have recently been approved to protect women against persistent infection from the most prevalent high risk HPV types, HPV 16 and 18 and CIN. Both vaccines are composed of noninfectious, recombinant HPV virus-like particles (VLPs) of the major capsid protein, L1. L1 has the intrinsic capacity to self-assemble into VLPs when expressed in eukaryotic cells. The advantage of these VLPs is that they are morphologically indistinguishable from authentic virions but they lack the viral genome. Because L1 VLPs mimic the natural virus structurally they are able to elicit high titres of virus-neutralizing-antibodies in animals and humans (Frazer 2004; Schiller and Lowy 1996).

Gardasil® is a quadrivalent vaccine, produced in yeast. It includes VLPs of HPV types 6, 11, 16, and 18 (Garland et al. 2007). Cervarix®, is a bivalent VLP vaccine

for HPV types 16 and 18 that is manufactured in an insect-cell system (Harper 2008). Research is also being conducted on therapeutic vaccines for women who have already contracted an HPV, but we discuss only prophylactic vaccines.

Though evidence indicates these vaccines are efficacious in preventing CIN, we show that the extent to which this is evidence of drug success depends on the social aims of the research. If, for example, one takes the goal of the research to be a reduction in cervical cancer morbidity and mortality among vulnerable populations, alternative evidentiary standards and methodological decisions would been more useful in helping to achieve that aim. We thus argue that the extent to which methodological and evidentiary decisions are justified depends partly on the degree to which they promote the social aims of the research. In particular, we examine how the social aims of the research help justify (1) framing of research problems and parameters for solutions, (2) evidentiary standards used in evaluating vaccine success and safety, and (3) clinical trial methodology.

Framing of the research problem and parameters for solution in vaccine development

One potential social aim of HPV research was to decrease cervical cancer morbidity and mortality. How might this aim be relevant to adopting parameters for vaccine development? As mentioned, the greatest incidence of cervical cancer occurs in developing countries. Since the introduction of routine screening programs with Papanicolaou tests in the 1960s and 1970s the incidence of cervical cancer has decreased in most industrialized countries, where it accounts for only 7% of all female malignancies (Safaeian et al. 2007; Parkin et al. 2005). In developing countries, however, where screening programs are less prevalent, cervical cancer accounts for 24% of all female cancers (Safaeian et al. 2007; Suba et al. 2006). In these countries, fewer than 50% of women affected by the disease survive longer than 5 years, while about 66% do so in industrialized nations (Franco and Harper 2005). Thus, if the aim of HPV research is to significantly decrease cervical cancer morbidity and mortality, then developing a vaccine that will work in developing countries is crucial to this goal.

In investigating possible solutions to this problem however, researchers fail to attend to the very different methodological criteria of testing efficacy or testing effectiveness of the possible vaccines. Evidence about efficacy is not sufficient to establish that the medical procedures in question will be *effective*, i.e., will work in real world conditions. Efficacy studies evaluate whether the experimental procedure generates specific therapeutic effects and thus they establish the extent to which a particular procedure is causally efficacious in treating or preventing the studied condition, under the controlled circumstances of the laboratory. But in practical contexts, like the ones usually present with developing medical intervention, a solution to the question of efficacy, what vaccine can be developed that will under some ideal protocol of use prevent HPV infection and cervical cancer, is adequate only if one does not take into account the social goals of the research. This is so because efficacy studies, despite their high internal validity, might not be very useful in guiding clinical care (Nallamothu et al. 2008; Cartwright 2007; Grossman

and Mackenzie 2005). Such internal validity might tell us little about how medical interventions perform in different real-world settings. If, on the other hand, the social goals of the investigation are taken to be relevant in guiding research, then the question of effectiveness, that is whether given the actual real world circumstances particular vaccine strategies will have the desired effect, becomes relevant.

The two vaccines now on the market present significant challenges to be useful in developing countries. First, these vaccines are expensive to manufacture because they are produced in eukaryotic cell cultures and need extensive purification. Second, they require refrigeration and thus are expensive to distribute, as they need a cold chain for storage. Third, three doses, over a six month period, are delivered by intramuscular injection, which increases the costs of production and distribution. Women in resource-poor countries, particularly those in rural areas, will lack access to medical facilities, decreasing the likelihood they will be able to receive all three doses. Fourth, they are most effective when given to females in early adolescence, but in many developing countries, cultural barriers make this a difficult group to enroll in vaccination programs. Finally, the vaccines are of little use to women who are already HPV- infected or who have already developed neoplasia (Hildesheim et al. 2007; Schiller and Nardelli-Haefliger 2006).

Now, one might argue that scientists cannot adopt research parameters in relation to the social aims of the research because researchers cannot always predict how medical interventions might work in the "real world." Even when researchers are able to foresee that a solution will not be completely effective in helping achieve a social aim, it may still be the "best available," given current scientific research. That is, scientists should adopt research parameters solely on the basis of whether they are the most epistemically promising.

At the time HPV vaccines were under development, however, researchers had a variety of options that would have increased the ease of preparation, stability of the components, and effectiveness of delivery. First, they could have used naked DNA that contained the L1 gene driven by a strong eukaryotic promoter. Naked DNA is easily prepared in large scale with high purity, is relatively safe, and can be used for repeat administration. Also, naked DNA vaccines are highly stable relative to proteins and can sustain high levels of antigen expression in cells. All of these characteristics make DNA vaccines cheaper in terms of ease of preparation, storage, and delivery (Moniz et al. 2003; Schiller and Lowy 1996).

A second option was to use live bacterial vectors such as live attenuated Salmonella strains. These vaccines can induce both mucosal and systemic immune responses and are able to express foreign antigens (Fraillery et al. 2007). They can be generated inexpensively and are likely to be potentially effective in a single dose. Moreover they do not require a cold chain (Fraillery et al. 2007). This type of vaccine would have been easier to distribute and administer in rural areas.

Another possibility was the oral delivery of VLPs in food, for instance, by generating transgenic plants that express VLPs (García Carrancá and Galván 2007; Schiller and Lowy 1996). Contrary to current parenteral vaccines, transgenic plants expressing recombinant vaccine immunogens are an inexpensive alternative given that edible plants can be grown locally and distributed easily without special training or equipment (Fernández-San Millán et al. 2008; Warzecha et al. 2003).

We claim that which of these avenues for vaccine development would have been best, or most justified, depends partly on the social aims of the research. If the aim of the research were to significantly decrease cervical cancer morbidity and mortality, it would have been more rational to use a vaccine technology more likely to be useful in the context of resource poor countries. If the aim of the research were, say, to produce a profitable vaccine, then this would justify developing a vaccine more likely to work in industrialized countries. The social aims of the research help justify the parameters that a successful vaccine must meet (as well as the decision about which research strategies are most likely to achieve them). Different aims will help justify different research parameters.

Now, one might argue that no particular social aims of research need to be endorsed, as multiple aims can be pursued simultaneously through a variety of empirically adequate research programs. Solomon (2001) advocates this approach. On Solomon's view, research effort should be distributed among the development of each type of vaccine to the extent that the research program is yielding empirical success (Solomon 2001, 32). This way, whether we value helping the most vulnerable populations or producing profits for drug companies, each empirically promising avenue of research will be pursued (solely on epistemic grounds).

While research on each of the different vaccine strategies is presently being conducted, it is unclear that decisions about which strategies to pursue can be made on the basis of empirical success alone. First, because there are limited resources, pursuing all empirically adequate possibilities may be difficult. More importantly, pursuing some vaccine development options may hinder work on others, even if they are empirically successful. The fact that efficacious prophylactic HPV vaccines already exist might make it more difficult for other vaccines to reach clinical trials and the market. If the public in industrialized countries perceives that current vaccines solve the problem of cervical cancer, public funding sources to develop alternative vaccines may be unavailable. Similarly, because of intellectual property constraints, competitive commercialization of other VLP-based vaccines might be difficult. Given the significant investments by Merck and GSK in the current vaccines, it is unlikely that they will be interested in the development of substantially different and cheaper vaccines (Schiller and Nardelli-Haefliger 2006). Thus, not all empirically adequate research avenues can be pursued simultaneously. Choices must be made about which properties are *necessary* for a successful vaccine to have. Making this decision rationally, however, involves endorsing and consulting particular social aims.

Evidentiary standards in vaccine testing

The social aims of research also play an important role in helping to justify evidentiary standards in vaccine testing. Randomized clinical trials, the main method for testing and evaluating medical procedures, are considered the gold standard (Sackett et al. 2000). Because such trials are carried out in highly controlled laboratory conditions, when designed and conducted appropriately, they give us evidence for the *efficacy* of such procedures. Indeed, results from major Phase II and III trials of the two HPV vaccines show they are highly immunogenic

and efficacious against CIN2/3 lesions and adenocarcinoma in situ (AIS). These lesions are the obligate and immediate precursors to invasive cancer. Evidence also indicates that the vaccines offer some protection against persistent HPV16 and/or18 infections to HPV naïve women. (Harper et al. 2006; Garland et al. 2007; Paavonen et al. 2007; The Future II Study Group 2007a, b).

But as we indicated earlier, evidence about efficacy is not sufficient to establish the effectiveness of medical interventions. Hence, clinical trials might be alternatively designed to obtain evidence of effectiveness. That is, they could be conducted under circumstances more closely simulating conditions that normally obtain for patients. This, too, would have potential drawbacks. Obtaining evidence of effectiveness involves allowing a host of complex variables to influence clinical trial experiments. This makes it far more difficult to isolate and identify causal relationships. As a result, the effectiveness measured can be due to other factors such as placebo effect, concomitant therapies, or social factors.

One option would be to require Phase IV clinical trials for drug approval in addition to Phase II and III trials. Phase IV trials would obtain evidence of longer-term effectiveness in real world conditions in addition to evidence of efficacy. Such a requirement before drugs are approved, however, could delay potentially helpful medical interventions.

Thus, researchers have a choice about the kind of evidence that is important to collect for drug "success." There are limitations to designing clinical trials that only test for efficacy, as well as drawbacks to only testing for effectiveness. Our claim is that the grounds for making this choice include the extent to which various evidentiary standards promote the social aims of the research. If the aim of the research is to have a vaccine that will be effective in certain real world conditions, then evidence of efficacy alone will be insufficient. Even if this social aim is ultimately outweighed by other epistemic or social values, such as the need to isolate causal relationships or get medical interventions into the market quickly, the justification for adopting particular evidentiary standards will rest on weighing these competing values. In the next section we show that the social aims of the research also play a role in justifying specific methodology adopted in the design of HPV clinical trials.

Methodological decisions in clinical trial design

The social aims of the research also help justify specific methodological choices in clinical trials. First, they have implications for the appropriate duration of clinical trials. The follow up for HPV vaccine studies have been relatively short (about 5 years). This is somewhat problematic insofar as part of the aim of the research is to create vaccines with long term protection against HPV. Of course, the value of having evidence of long-term HPV protection must be weighed against the value of getting the vaccine quickly on the market. Balancing these interests, however, involves weighing the social aims at stake in the research. The extent to which methodological decisions about the duration of clinical trials are justified involves social values.

Second, the social aims of research help justify inclusion and exclusion criteria. Like typical efficacy studies, clinical trials for HPV vaccines used narrow

enrollment criteria such as healthy women aged 15–26 years, with a particular number of lifetime sexual partners before study enrollment, adequate contraception over the vaccination period, cytologically negative, and seronegative for HPV-16 and HPV-18 antibodies. With narrow eligibility criteria, we cannot determine whether the seroconversion rates, antibody titres, and efficacy rates will be as high in unselected populations of women (Kahn and Burk 2007). When taking into account women representative of those in real world settings, such as women who did not follow the protocol adequately or did not complete the planned vaccination regimen, some studies have reported only a 17% overall reduction in CIN after administration of the quadrivalent vaccine (The Future II Study Group 2007a, b). How narrow the selection criteria ought to be depends on weighing the social, as well as epistemic, consequences of adopting such criteria.

To the extent that the aim is to measure whether the vaccine will work for the most vulnerable populations, wider inclusion criteria may be more justified. After all, women in non-industrialized countries who are most likely to develop and die from cervical cancer are also likely to fail to meet one or more of the narrow inclusion criteria for the vaccine trials. These women are more likely to be infected with the human immunodeficiency virus (HIV) and evidence indicates that HIV positive women are at an increased risk of developing CIN and cervical cancer (Adam et al. 2008). They are also more likely to have endemic infections, such as hepatitis B or malaria that chronically alter the immune system and may modify the patterns of immunogenicity or affect the safety profile of HPV vaccine. Additionally, there may be significant differences in HPV vaccine immune responses among malnourished, compared with better-nourished, populations (Pagliusi and Teresa Aguado 2004).

Thus, clinical trials that have "healthy" as an inclusion criterion fail to collect relevant data on populations of women most at risk for cervical cancer. Again, this is a problem insofar as the aim of the research is to decrease cervical cancer morbidity and mortality in those populations.

Third, the social aims of the research have implications for what will count as a representative group of subjects included in clinical trials. For example, to what extent should a pool of subjects be heterogeneous or ethnically diverse and what sort of diversity is necessary? In HPV vaccine clinical trials, the proportion of subjects who reported they were black or Hispanic in these studies was small (Kahn and Burk 2007). This could be problematic given the fact that Hispanic women are diagnosed with cervical cancer almost twice as often, and African American women more than 1.5 times as often as non-Hispanic white women (Downs et al. 2008). If the aim is to reduce cervical cancer in the most vulnerable populations, then their representation in clinical trials is crucial to ensure that ethnicity does not affect the efficaciousness of the vaccine.

Fourth, the social aims of the research help justify which endpoints or surrogate endpoints should be adopted in clinical trials. HPV vaccine trials use CIN 2+ as a surrogate endpoint, given that for both practical and ethical reasons, researchers cannot and ought not to wait to see if subjects actually develop cancer (Kahn and Burk 2007). This decision is justified insofar as these are accurate predictors of cervical cancer and insofar as the aim of the research is to reduce cervical cancer

morbidity and mortality. If the social aim of the research were, for example, reducing the incidence of genital warts, then this would be reason to adopt a different endpoint. Thus, whether a particular endpoint or surrogate endpoint is justified depends partly on the social aims of research.

Finally, the social aims of the research can help justify clinical trial locations. Both the bivalent and the quadrivalent vaccine have undergone phase III clinical trials in North America, Latin America, Europe and the Asian Pacific region. Despite the fact that age-standardised HPV prevalence is significantly higher in sub-Saharan Africa than in other world regions, vaccine studies were not done in these countries. This is particularly significant given evidence that suggests heterogeneity in HPV type distribution among women from different populations (Blossom et al. 2007; Clifford et al. 2005). Studies indicate that HPV-positive women in sub-Saharan Africa are significantly more likely to be infected with high-risk types of HPV other than HPV16 than were women in Europe. HPV35, HPV45, HPV52, HPV56, and HPV58 are all more common in HPV-positive women in sub-Saharan Africa than in Europe. Indeed, HPV35 is as prevalent as HPV16 in sub-Saharan Africa, but four to five times less prevalent than HPV16 in other regions (Clifford et al. 2005). Regional differences, although somewhat weaker, exist not only in cases of HPV infection but also in cases of cervical cancer. A smaller proportion of cases in sub-Saharan Africa and Asia are associated with HPV16 compared with those in Europe or North America (Clifford et al. 2005). Hence, HPV vaccines for types 16/18 might have different efficacy measures in clinical trials conducted in different countries (Muñoz et al. 2004). Thus, the decision about where best to conduct clinical trials depends partly on the social aims of the research (e.g., which populations are being targeted).

We have shown that methodological decisions about the duration of the study, subject selection criteria, diversity of subjects, choice of surrogate endpoints, and location of clinical trial sites are justified partly by the social aims of the research. Some methodological choices will promote specific social aims better than alternatives. Making good methodological decisions in the design of clinical trials thus depends on social, in addition to epistemic, values.

Normative implications and conclusions

The case of the HPV vaccines shows that the specific social aims of biomedical research play a role in justifying research decisions in both drug development and testing. Such aims can be relevant to the choice of research strategies, evidentiary standards, and methodologies. If these decisions are made in relation to social aims, researchers will be more likely to produce medical interventions that are more socially relevant and effective.

In these ways, social values can play important and appropriate roles that go beyond merely determining what ought to be studied or funded. That is, they are sometimes necessary to making fully grounded methodological decisions. Thus, we join those philosophers of science who argue that ethical and social values can play inescapable and necessary roles in science, at least in those research contexts that

are related to public policy (Longino 2002; Douglas 2007; Kourany 2003). This is not to say that social values stand as evidence for the truth of, for example, claims about the causal mechanisms of HPV or the efficacy of a particular drug. They can, however, provide us with reasons to take certain research strategies or methodologies to be better than alternatives. Thus, our arguments are also consistent with the position, taken by several philosophers of science, that social value judgments need not undermine the objectivity or rationality of science (Longino 2002; Dupré 2007). Indeed, we are claiming that they can increase the rationality of some standards of evidence and methodological decisions.

If we are correct that the social aims of research affect decision-making, this raises the question of which social values and aims should be endorsed and who, exactly, should be making such decisions. Clearly, if social values are at stake, we must strive to appeal to values that are well supported. But, given the existence of multiple competing social values, how is this best accomplished? While we cannot develop or defend here complete answers to these questions, we draw some tentative normative lessons from the HPV case.

Obviously, scientists have an important role in helping to endorse particular social aims of a research program and making judgments about how best to promote those aims. Biomedical researchers have the scientific expertise relevant to determining how social aims might be best conceived in relation to particular health problems, and how those can be promoted given the current state of biomedical research. For example, biomedical researchers would be in the best position to know which current vaccine types are possible and most promising, or which surrogate endpoints are appropriate.

Yet although scientists need to be involved in identifying, endorsing, and promoting the social aims of research, it is not clear that they can or should be making such judgments alone. As Kitcher (2001) points out, the social aims of research (in order to be justified) should represent the interests of all stakeholders. Scientists may be unaware of all the interests at stake, and they may lack important information relevant to how they could best promote social goals. Biomedical researchers working on the HPV vaccine may know little about the social conditions in rural Africa that impose limitations on successful vaccine delivery. Thus, in order to promote more socially relevant science, there need to be mechanisms for scientists, social scientists, ethicists and policymakers to collaboratively reflect on the social aims of research and how best to promote them.

One mechanism for such collaboration is in the writing and evaluation of grant proposals. When applicable, principal investigators should be required to identify the social aims of their research, and their proposed methodology should be justified in relation to not only to epistemic goals, but also to social ones. Grant reviewing teams should include diverse individuals with relevant expertise. In the HPV case, insofar as the aim of the research is to significantly reduce cervical cancer among vulnerable populations, this might include microbiologists, immunologists, sociologists, epidemiologists, public health professionals, and ethicists. In evaluating the intellectual merit of research programs, reviewers need to consider the extent to which the social aims of the research are justified, as well as the extent to which the proposed research strategies, standards of evidence, and other methodological

choices promote those aims better than alternatives. The interests and expertise that will need to be represented in the review process will depend partly on the nature and content of the particular research project.

While we cannot provide a full account of how the social aims of research might be endorsed or promoted here, it is clear that a discussion about which social aims should be endorsed in particular research contexts and who should make those decisions is a conversation that is appropriate and necessary. It is a discussion that will not take place if scientists continue to assume that values have no business in science.

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