ORIGINAL ARTICLE

Sex-differential responses to preventive health interventions

Maybe we treat boys and girls differently when we treat them equally? – secondary publication

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ABSTRACT

It is well recognised that boys and girls differ with respect to morbidity, for instance boys more often suffer from respiratory infections and asthma, whereas girls are more susceptible to celiac disease and insulin resistance/type II diabetes. Nonetheless, there are very few studies which have addressed the potential differences in boys' and girls' immune systems. From our perspective of long-term research in low-income countries, it is problematic that we implement preventive health interventions and treatments which influence the immune system without investigating whether there are sex-differences in the response to these interventions.

Within the current health system it is indisputable that boys and girls should be treated the same way. The intention is that they should have the same opportunities. This had been interpreted as if they should receive the same treatment. But equal treatment is not necessarily synonymous with equal opportunities, if the treatment has different effect in boys and girls. In Guinea-Bissau, our research in vaccines and vitamin A supplementation has documented that there are significant sex-differences in the response to these interventions. In low income countries with high child mortality this can lead to considerable shifts in female and male mortality within a population.

ROUTINE VACCINATIONS IN CHILDHOOD

In 1989, the World Health Organisation (WHO) introduced a new high-titre Edmonston-Zagreb measles vaccine in low income countries. The vaccine had been developed with the aim of introducing protective immunity early in life, in the presence of maternal antibodies. It was at least as protective against measles as the previous standard Schwarz measles vaccine. We investigated the effect of the new vaccine in studies in Guinea-Bissau and Senegal. Surprisingly we found that the new high-titre measles vaccine was associated with two-fold higher female mortality compared with the standard measles vaccine. Girls who received the new vaccine had two-three times higher mortality compared with boys who received the new vaccine [1]. The findings were confirmed by other groups and as a consequence WHO withdrew the high-titre vaccine in 1992. Our results indicated that had the vaccine not been withdrawn, it would have resulted in at least half a million additional female deaths every year in Africa alone.

The discovery of these dramatic sex-differences in response to a vaccine made us investigate the potential sex-differences in response to other vaccines. Surprisingly, the standard measles vaccine was associated with 40% lower mortality in girls compared with boys [2]. Subsequent studies have shown that the BCG vaccine likewise is associated with decreased female mortality [3]. In contrast, the diphtheria-tetanus-pertussis (DTP) vaccine seems to be associated with higher female than male mortality [3, 4]. All these effects are most pronounced when the vaccine in question is the last vaccine received. The latter observation made us reinvestigate the high-titre measles vaccine data. The high-titre measles vaccine was given earlier in life than the standard measles vaccine, thus, many children had received one of more DTP vaccines after the high-titre measles vaccine. The reanalysis of our data showed that the negative effect of the high-titre measles vaccine was only seen among girls who had received DTP vaccine after their measles vaccine, whereas there was no negative effect among girls who had not received a DTP vaccine [5]. Thus, the observed increased mortality after high-titre measles vaccine may in fact have been due to increased female mortality after DTP vaccine. Hence, the vaccine may have been withdrawn for the wrong reasons. However, it was still good that it was withdrawn, since it changed the sequence of vaccinations and resulted in more children having DTP as their last vaccine – and thereby higher female mortality.

In conclusion our results suggest that live vaccines such as standard measles vaccine (and maybe also high-titre measles vaccine) and BCG vaccine are associated with decreased female mortality whereas the inactivated DTP vaccine is associated with increased female mortality. Hence, girls seem to be more susceptible to positive as well as negative *non-specific effects* of childhood vaccination on mortality.

As the non-specific effects of vaccines on mortality can be both positive and negative they can be difficult to disentangle, since they are likely to counterbalance each other. If all vaccines are analysed simultaneously in a statistical model without analysing boys and girls separately, no pattern is likely to emerge. The pattern only becomes apparent when the vaccines are analysed separately in the periods in which they are the last vaccines received and stratified by sex. Few groups have analysed vaccination data this way and our results still stand alone. However, we have analysed data from other groups and found similar sex-differential effects.

VITAMIN A

Vitamin A supplementation of children aged six months to five years of age is associated with a 23-30% reduction of all cause mortality in low income countries [6]. Vitamin A supplementation might also be beneficial when given at birth, at least in some studies, whereas there is no beneficial effect when given between one and five months of age [7]. Only few studies have reported the results by sex. Based on the literature and our own results, we have put forward the hypothesis that vitamin A supplementation is more beneficial for infant boys than girls and in some situations it may even be harmful for girls. The first large randomised vitamin A trial, conducted by the famous ophthalmologist Sommer and his colleagues,

We dress them differently. Should they still receive the same health interventions?

reported that while vitamin A supplementation reduced mortality among 0-11 month-old boys by 40%, it was associated with increased mortality among their female peers [8]. The two studies that have addressed the effect of vitamin A supplementation at birth and reported data by sex, both found a significant beneficial effect among boys, but less or no effect among girls [9, 10].

We have therefore focused on potential sex-differences. In our first study of the effect of vitamin A supplementation on the antibody response to measles vaccine, vitamin A was associated with significantly increased measles-specific antibody responses among boys, but had no effect among girls [11]. We have recently shown that a lower dose of vitamin A than the one currently recommended was associated with lower mortality in girls, but a tendency for higher mortality in boys [12]. In conclusion, there seem to be sex-differences in the response to vitamin A supplementation with better effect among boys than girls.

DISCUSSION

Our studies of childhood vaccines and vitamin A supplementation have consistently shown sex-differences in the response to these very common health interventions. If our observations are correct, then acknowledging such sex-differences, pursuing the underlying mechanisms in further research and optimising the ideal intervention programmes for both sexes could lead to important changes in the health intervention programmes in low-income countries and decreased child mortality.

Our research has focused on low-income countries, but similar vaccines are used in high-income countries. Fortunately, it is unlikely that we would be able to observe sex-differences in mortality in response to vaccinations in high-income countries. However, our observations in low-income countries have encouraged us to study potential sex-differences in morbidity in response to vaccinations. These observations should also encourage other researchers to look for sex-differences in response to other interventions. This is an example of how research in low-income countries under extreme conditions with many infectious diseases and high mortality can generate results which may prove of value in high-income countries as well, adding yet another argument for conducting research in low-income countries.

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The manuscript is based on more references, a full list of references can be obtained from the authors.