Reviewer’s report

Title: Newborn screening for congenital adrenal hyperplasia in Tokyo, Japan from 1989 to 2013: epidemiology and efficiency of the screening: a retrospective population-based study

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Reviewer: Rachel Knowles

Reviewer’s report:

The authors describe a retrospective review of cases of congenital adrenal hyperplasia identified during the first 14 years of implementation of a newborn screening programme in Tokyo. The authors’ aim is to describe the epidemiology of CAH diagnosed after screening and the performance of the screening programme. They suggest that this may differ from similar studies in other countries due to ethnic differences. The study is of some interest as an observational study of CAH screening in Tokyo but there is little evidence provided to support the generalisability of the results to all of Japan. Furthermore it fails to report any screening programme performance parameters other than positive predictive value, although there is significant detail about the actual 17OHP test process.

Background:

Minor essential revisions:

i. In the background section, the authors refer appropriately to a previous paper describing newborn screening programmes in Japan (ref 3), however it would be helpful if there were more information about the Japanese screening programme for CAH in this paper, as well as a statement about whether the Tokyo programme is typical of newborn screening elsewhere in Japan or East Asia.

Methods:

Major Compulsory Revisions:

i. The authors describe the 17OHP measurement in sufficient detail however they should provide more detail on the age at newborn screening as this may have an important impact on the effectiveness of the screening programme and its ability to identify babies at risk prior to collapse, as well as its comparability with other programmes.

ii. Table 1 suggests that screening may be undertaken at 5-10 days of age, however in the body of the text, the authors state only that blood sampling was performed at ‘5 days or after’; there is no information about the spread of ages at screening. Such data should be added.

iii. The authors should clearly state whether the Tokyo screening programme is representative of newborn CAH screening throughout Japan and East Asia, and therefore whether the findings of the study are generalisable.
iv. The authors provide very little information about the sources of data, data variables and quality of the data collected in the follow-up survey. Were these data complete for every child and were the sources of data reliable?

Results:

Minor essential revisions:

i. The authors’ presentation of their results is somewhat confusing. Detailed information is present within the tables but an improvement would be to provide additional summary text interpreting the tables and figures, and thus to draw the reader’s attention to the key points presented.

Major Compulsory Revisions:

ii. To more clearly present their findings, I believe the authors should begin by describing the characteristics of the children in the population undergoing screening (e.g. % term/preterm, median birth weight, median age at screening) to provide a baseline understanding of the population screened. They should then describe the number diagnosed with CAH and the characteristics of those with positive screen results and an eventual CAH diagnosis, e.g. proportion/number with 21OHD or other forms of CAH, sex ratio, etc. A comparison could then be more clearly drawn between the background population and those with positive screen results and/or with CAH diagnoses, in particular with regard to birth weight and gestation.

iii. The authors report the number of babies screened but should state whether screening coverage was complete, as it is unclear whether the incidence of 1:19,934 refers to 1 diagnosed case per 19,934 children screened or 1 diagnosed case per 19,934 births in Tokyo.

iv. The authors provide positive predictive value and false positive rates but should also describe in the text more detail of the repeat testing required (which appears considerable).

The figures presented appear to be genuine and believable and there is no evidence of manipulation.

Discussion/conclusions:

The authors highlight the 17OHP screening test as a primary concern for future screening programmes to address, which is accurate and has been highlighted also by studies from other countries.

Major Compulsory Revisions:

i. The authors make several statements in their discussion that do not appear to be well-supported by the data presented earlier in the paper. In the first paragraph of the discussion, they state that the population screened were homogeneous in race/ethnicity but they should provide evidence to support this.

ii. The authors further state a primary aim of screening was to prevent adrenal crises, so they should present any data relating to adrenal crises within their population.
iii. The authors appear to assume that there is no migration in or out of Tokyo (such that newborns may have presented clinically with CAH to hospitals outside of Tokyo), so should provide evidence to suggest that the population is stable in the newborn period and that they have good population coverage.

Describing limitations of the study:

Major Compulsory Revisions:

i. The authors acknowledge the lack of follow-up of negative screens to identify false negative results as a limitation, however they should describe why they made no attempt to identify false negative cases (‘missed’ diagnoses amongst living or dead children) within the screened population. The lack of follow-up data for negative cases means they cannot assess screening programme performance fully as they cannot report sensitivity nor specificity.

ii. The authors should discuss the large number of repeat tests required as an additional limitation to screening. What are the psychological and cost implications of repeating screening in this population?

iii. The authors state that no deaths were reported but should provide evidence that the passive reporting by paediatric endocrinologists was sufficiently well-conducted to have accurately identified such cases. As studies in other countries suggest that deaths may occur before diagnosis or without diagnosis, it seems unlikely that passive reporting of deaths would have completely identified deaths. The authors could discuss this as a limitation or provide evidence that demonstrates that reporting of deaths was accurate and complete.

The authors make appropriate reference to previous studies in the East Asia region and elsewhere.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.