Reviewer's report

Title: Community acquired bacterial meningitis in Cuba: a follow up of a decade.

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Reviewer: Annunziata Faustini

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COMMENTS TO THE AUTHORS
The authors reported the incidence and the case fatality rate (CFR) of bacterial meningitis (BM) in Cuba in the period 1998 – 2007 using data from an enhanced surveillance system, which began in 1998. Distributions of BN according to pathogenic bacteria and patients’ characteristics (age and gender) were described as well as geographical and seasonal spread of BM cases. Predictive factors of mortality were explored including timing of medical consultation and hospitalisation. The authors found an incidence as high as 5.5/100,000 people in 1998 that decreased substantially to 3.3/100,000 in 2007. The greatest reduction was observed in 1-5 year old children and in 84+ year old people, the same groups that showed the highest incidence at the beginning. In most cases (55%) the pathogenic agent was not detected, and meningitis was confirmed on the basis of cerebrospinal fluid (CSF) cyto-chemical parameters. Among the other types of BM, Streptococcus pneumoniae was the most frequent (24%), followed by Neisseria meningitidis (8%), other bacteria (7%) and Hib (6%). The overall CFR equalled 24%, increased proportionally with the patients’ age and did not vary substantially in the study period. Both the incidence and the CFR showed the highest values in three central provinces. The highest peak was in September, but peaks were observed in all seasons. Delayed medical consultation, being a housewife, retired, unemployed, or imprisoned and having been infected by S. pneumoniae were factors associated with BM patients’ death.

MAJOR COMMENTS
The paper exhaustively describes BM epidemiology and it makes interesting suggestions for data analysis but it does not thoroughly pursue the declared aims, due to an unclear definition and to analytical methods that are unable to answer the research questions properly.

THE AIMS OF THE PAPER
The stated aims of the paper are to characterize epidemiological features of BM and to assess risk factors for incidence and mortality in the abstract, while in the introduction the authors define a second aim to report the BM surveillance experience in Cuba.

Nevertheless, assuming the authors stated three aims, important methodological limits are raised both in analyzing risk factor and in evaluating the surveillance
impact. The former analysis was performed for mortality only and the crude estimate of the relative risks (RR) are not suitable to analyse the complex relationships between the variables. For example, the analysis for the variable of retirement is biased by old age as unemployment is strictly associated with the youngest ages; moreover, being a housewife is a proxy of caring for children and ill relatives, but it is not a risk factor itself. On the other hand, if the authors wanted to analyse the effectiveness of the enhanced BM surveillance in Cuba, they must describe the surveillance characteristics better since they influence reporting completeness and possible selection. I mean that an integrated surveillance as the authors described the one in Cuba since 1998 uses data from more than one independent system already in operation, which usually has a minor impact on the data reported, while an “enhanced surveillance” as I think the Cuban experience can be defined, introduces more specific data for each case of a specific disease, from the laboratory or patients or health care operators, to those routinely collected [these definitions have been given by the WHO since 1997]. In this case a possible increase in cases is reported at the beginning, that should be explored by a sensitive analysis. This should compare the incidence estimates with others obtained, including the suspected BM cases that were not tested with the cerebrospinal fluid (CSF) test and the patients discharged from hospital with a BM diagnosis possibly not reported to surveillance e.g. because they died during hospitalisation.

ANALYSIS OF TREND AND ITS CAUSES

A formal analysis for trend should be carried out to take into account the annual variability of the rates, not only the difference between the extreme points of the period. Trend analysis may be carried out using many statistical packages including EpiInfo version 6.

Trends should be analysed for both incidence and mortality. On the basis of crude data a decrease was observed for incidence but not for CFR. To better discuss this point a time variability of risk factors could be important, with special attention to those related to health care and the pathogens.

With regard to these factors, the authors conclude for an important role of vaccination campaigns in reducing incidence, but these campaigns were roughly described only in discussion. Therefore, we do not know the target age of vaccinated people, the year when each campaign started, or the coverage of target population and its trend, i.e. the main characteristics of vaccination that could have effectively influenced the BM incidence trend. Even assuming the effectiveness of this intervention, it is expected to be associated with more of a decrease in children’s cases than in the oldest group (84+ years) during the 10-year follow-up. Finally, alternative explanations for the decrease were not hypothesised at all. An important and highly probable reduction in the CSF test in very old patients could have contributed to a decreased incidence of confirmed BM, after the first surveillance period.

GEOGRAPHICAL DISTRIBUTION

For the geographical data also the authors have to answer the question: which
other factors showed
a similar geographic profile? An ecological analysis of the risk factors, for
example vaccine
coverage, health services availability and delay in detecting the disease could
help to better explore
the hypothesis that prevention and health care could influence incidence and
death.
But other factors also should suggest an explanation about the geographical
distribution of the disease. If data are available from surveillance, I would suggest
an ecological analysis specially for factors already known to be associated with
high transmission; house crowding or other social indicators, population mean
age and health services availability / accessibility could help in exploring the
factors associated. Finally, the geographical distribution of the pathogenic
bacteria could also suggest a hypothesis for the incidence variability between the
areas.

RISK FACTORS
The patient characteristics (age, gender) as well as the pathogenic bacteria,
though reported in descriptive terms, have to be included in the regression
analysis as risk factors of both incidence and mortality; in fact, their influence not
only on the disease outcome but also disease occurrence is well known. In other
words the RRs have to be estimated for these characteristics. On the other hand,
the reciprocal association of risk factors is so important that a multivariable
approach is essential in estimating the strength of the association, to control the
confounding effects of the other variables and to assess the interaction between
variables. To add another example to those already discussed in the paragraph
about the aims of the paper, the higher CFR in the females could be due to a
longer life expectancy for females, a multivariable analysis (or at least a
standardization by age) could avoid this bias. I suggest that the authors consider
the paper by Barquet et al. JAMA 1997 titled, “Prognostic factors in
meningococcal disease” that is, in my opinion, a very useful example of a
predictive model of BM outcome and the paper by Sàez-Llorens et al in the
Lancet 2003 titled, “Bacterial meningitis in children” that thoroughly analyses the
prognostic factors in children.

The high proportion of BM of unknown aetiology could influence the association
with prognostic factors; a sensitivity analysis comparing BM of unknown and
known aetiology could help to better address the interpretation of risk factors
analysis.
A finally remark, but only in terms of personal curiosity, is why the authors did not
analyse the total time lapse from symptoms onset to starting therapy, adding the
two timing components they studied here: the delay of medical consultation and
the hospitalisation delay.

DISCUSSION
Discussion about incidence and mortality is correctly addressed to comparing
estimates in Cuba with those found in North and South America countries. Nevertheless, I think that the incidence data presented in the paper cannot be discussed simply as they went from a cross-sectional survey. This way the authors waste the opportunity to deal with temporal variations of rates that should be compared with trends observed in other experiences, with particular attention to vaccination introduction.

Focusing on climatic and geological differences to explain the geographical differences of incidence is surprising, especially as they did not explore the factors related to infection transmission that are more related with social and behavioural characteristics of people.

Even the observations about vulnerability due to underlying conditions are, in my opinion, supported very poorly by data and analysis carried out by the authors.

MINOR POINTS

The age groups for infants and children should be <1 and 1-4 to allow comparisons with other papers, which use 5 or 10 year age groups.

If information on the onset date were obtained from the relatives, it could be biased selectively for the more seriously ill patients. This point should be addressed in discussion.

When the distribution variable analysed is binary, reporting both modality percentages is redundant.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests