The proverb "Words are like cherries", meaning that when you start talking subjects pop up and you end up with long conversations, just like cherries coming out of the plate in chains when you pick one, may also be applied to epidemiological research. A sequence of epidemiological studies, each being drawn from the previous, is presented as an example of how each investigation may raise new questions to be addressed in following studies.

This description stresses the need for appropriate planning and the usefulness of pilot testing to depict inadequacies that can hardly be anticipated without field work. I intend to illustrate how epidemiological research can provide a deep approach to research questions, as long as findings are properly interpreted and suboptimal methodological options are taken into account in future investigations.

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This hypothesis was tested when the To quantify the To compare the recall of antimalarial treatments using two versions of a questionnaire in which the answering options are presented in a different order. To describe the use of antimalarial drugs, antihistaminic drugs and prednisolone in malaria episodes (see Appendix 2). *

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Objective</th>
<th>City, country</th>
<th>Participants</th>
<th>Main results</th>
<th>Questions raised/ comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falcao et al, 2003¹</td>
<td>To quantify the prevalence of self-reported drug allergy.</td>
<td>Porto, Portugal 2001</td>
<td>University students from public and private schools, including health and non-health related courses (n = 2150, 67.6% females).</td>
<td>Life prevalence of drug allergy (≥1 episodes): 7.7%. b-lactams (3.1%) and NSAIDs (2.1%) were the most frequently involved drugs.</td>
<td></td>
</tr>
<tr>
<td>Lunet et al, 2005²</td>
<td>To quantify the prevalence of self-reported drug allergy.</td>
<td>Maputo, Mozambique 2003</td>
<td>University students from a private school, including health and non-health related courses (n = 447, 55.3% women), and non-teaching staff (n = 62, 56.5% females).</td>
<td>Life prevalence of drug allergy (≥1 episodes): 25.0%. Chloroquine (11.8%), b-lactams (3.9%), aspirin (2.8%), and co-trimoxazol (2.2%) were the most frequently involved drugs.</td>
<td>The prevalence of self-reported allergy to chloroquine was higher than expected.</td>
</tr>
<tr>
<td>Gama et al, 2008³</td>
<td>To quantify the prevalence of chloroquine-induced pruritus and its associated factors.</td>
<td>Maputo, Mozambique 2004</td>
<td>University students from a private school, including health and non-health related courses (n = 488, 65.0% females).</td>
<td>Chloroquine allergy was more frequent in Blacks (18.0% vs. 3.2%), in the staff (24.2% vs. 11.0%), and increased with age. No such pattern was observed for allergy to drugs other than chloroquine.</td>
<td>Different pattern of association with socio-demographic factors were observed for self-reported allergy to chloroquine and to other drugs. The frequency of chloroquine-induced pruritus was similar to the prevalence of self-reported allergy to chloroquine.</td>
</tr>
<tr>
<td>Lunet et al, 2008⁴</td>
<td>To describe the use of antimalarial drugs, antihistaminic drugs and prednisolone in malaria episodes (see Appendix 1). *</td>
<td>Maputo, Mozambique 2006</td>
<td>University students from a private school, including health and non-health related courses (n = 504, 60.8% females).</td>
<td>The recall of quinine utilization was higher with the questionnaire version displaying quinine at the top of the list of options (19.5% vs. 11.6%), and similar results were observed for artemisinine/artesunate (16.5% vs. 7.3%).</td>
<td>The use of antihistaminic drugs and prednisolone during malaria episodes was less frequent than expected.</td>
</tr>
</tbody>
</table>

The proportion of subjects reporting to have used chloroquine before was 67.3%, from which 25.9% reported episodes of intense pruritus associated with chloroquine, supporting the hypothesis that the terms “allergy” and “pruritus” may have been interpreted as interchangeable by the participants, which could explain the unexpectedly high prevalence of self-reported chloroquine allergy observed in the first survey. Further research, namely qualitative, could contribute to further understand this phenomenon.

Surprisingly, the use of antihistaminics and prednisolone in the latest malaria episode was reported by only 1.3% and 1.9%, respectively.

The more plausible explanation for these low prevalence estimates is the fact that the questionnaire referred to drugs used...
least once. The proportion of drug use in 2004 and 2006 was compared with the $\chi^2$ test, or the Fisher exact test when appropriate.

The reported frequency of antihistaminic use during the latest malaria episode was substantially higher in the 2006 survey (17.7% vs. 1.3%, $p<0.001$), but no statistically significant differences were observed for prednisolone (1.5% vs. 1.9%, $p = 0.70$). In the survey performed in 2006, the proportion of subjects using chloroquine in the treatment of malaria was 57% when the latest episode took place before 2004, and 42%, 18% and 12% in the episodes occurring in 2004, 2005 and 2006, respectively, reflecting the replacement of chloroquine by artemisin-based combination treatments as first-line therapy for falciparum malaria in all endemic areas in Africa. Among the subjects who had their latest malaria episode before 2004, the prevalence of antihistaminic drug use was 17.7%, and 2.3% of the participants used prednisolone in association with the antimalarial drugs.

The differences observed in responses to these two questionnaires of different structure are much larger than could be expected given the results from previous studies showing the variation in the completeness of ascertainment of drug exposure according to how the participants are questioned. We hypothesized that the underreporting trend could have been further increased by the fact that respondents tend to choose the first response options when questions are presented visually (as in self-administered questionnaires), since the drugs with no antimalarial effect were placed at the end of the list. We could expect that after selecting an antimalarial drug most subjects did not read the rest of the options. This hypothesis was also tested in the 2006 survey, using an experimental design to compare two alternative versions of the questionnaire, differing only in the order in which each proposed drug was presented in the response options (quinine and most frequently used drugs presented first vs. less frequently used drugs first and quinine at the end). This analysis showed that the first antimalarial drugs being presented as answering options were more likely to be selected.

Taken together, these results show that symptomatic treatment of itching is more likely to be recalled when a specific question is placed for antihistaminic drugs and most of the times ignored when the answering option for antihistaminic drugs is presented together with antimalarial drugs.

The proverb “Words are like cherries”, meaning that when you start talking subjects pop up and you end up with long conversations, just like cherries coming out of the plate in chains when you pick one, may also be applied to epidemiological research. Here I presented a sequence of epidemiological studies, each being drawn from the previous, as an example of how each investigation may raise new questions to be addressed in following studies.

To some extent, this example may be seen as an exercise of trial and error, which rarely can be conducted by a single researcher or research group due to the lengthy and complex nature of epidemiological research in general, stressing the need for in depth knowledge of the study subject, appropriate planning and pilot testing. The conduction of small-scale tests of the methods and procedures to be used on a larger scale epidemiological research is an important component of the research protocol, useful to depict inadequacies that can hardly be anticipated without field work.

This “chain” of studies, however, may also be described as an example of how epidemiological research can be conducted with reasonable depth, capitalizing a proper interpretation of the findings and the need to take consequences of suboptimal methodological options into account on new investigations.

### Appendix 1

Structure of the questionnaire used in the 2004 survey to evaluate malaria treatment (including antimalarial drugs, antihistaminic drugs, and prednisolone).

<table>
<thead>
<tr>
<th>1. Did you ever have malaria?</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\square$ no</td>
</tr>
<tr>
<td><strong>If you answered no, please go to question 2</strong></td>
</tr>
<tr>
<td><strong>If you answered yes, please answer the following questions</strong></td>
</tr>
<tr>
<td>1.1. How many times did you have malaria in your life?</td>
</tr>
<tr>
<td>1.2. The latest time you had malaria, which drugs did you take for treatment?</td>
</tr>
<tr>
<td>Quinine</td>
</tr>
<tr>
<td>Chloroquine</td>
</tr>
<tr>
<td>Artemisinin/artesunate</td>
</tr>
<tr>
<td>Halofantrine (Halfan®)</td>
</tr>
<tr>
<td>Mefloquine</td>
</tr>
<tr>
<td>Sulfadoxine-pyrimethamine (Fansidar®)</td>
</tr>
<tr>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Clindamycin</td>
</tr>
<tr>
<td>Antihistaminic drugs (e.g. clorfeniramine, loratidine, etc.)</td>
</tr>
<tr>
<td>Prednisolone</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Please specify which other drug(s)?</td>
</tr>
</tbody>
</table>

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## Appendix 2

Structure of the questionnaire used in the 2006 survey to evaluate malaria treatment (including antimalarial drugs and antipruritic drugs separately).

1. Did you ever have malaria?
   - [ ] no  
   - [ ] yes

   *If you answered no, please go to question 2  
   If you answered yes, please answer the following questions*

1.1. How many times did you have malaria in your life?

1.2. In which year did you have malaria for the latest time?

1.3. In the latest time you had malaria, which drugs did you take for treatment?
   *Please read all the drugs in the list and select those that you took in the latest time you had malaria  
   You may select more than one option*

   - Quinine
   - Chloroquine (Resochina®)
   - Sulfadoxine-pyrimethamine (Fansidar®)
   - Amodiaquine
   - Halofantrin (Halfan®)
   - Artemisinine/artesunate (Arinate®)
   - Mefloquine
   - Lumefantrin+Artemeter (Coartem®)
   - Tetracyclines/doxycycline
   - Clindamycin
   - Other

   Please specify which other drug(s)? _______________________________

1.4. In the latest time you had malaria, did you take any of these drugs?
   *Please select those that you took in the last time you had malaria  
   You may select more than one option*

   - Antihistaminic/antiallergic drugs (e.g. chlorpheniramine, loratadine, Claritine®, etc.)
   - Prednisolone
   - Other

   Please specify which other drug(s)? _______________________________

### References