Reviewer's report

Title: Epidemiological characteristics and societal burden of Varicella Zoster Virus in the Netherlands

Version: 1 Date: 12 December 2011

Reviewer: Bernhard Ultsch

Reviewer's report:

Major Compulsory Revisions

1.1. Abstract:
1.1.1. Please state the objective of this study clearly in the Background section.
1.1.2. Next to last sentence: “67.8% of the patients received medication”. Please state on which patients you are talking about.
1.1.3. 1st sentence in conclusion, does not fit to actual results

1.2. Background:
1.2.1. Definition of PHN. How many month after HZ rash onset you count cases as PHN cases?
1.2.2. 2nd paragraph, 1st sentence: I’m not sure, whether all cited studies really investigate the „societal burden of VZV-related complications“ please check refs.
1.2.3. 2nd paragraph, 2nd sentence: This sentence might be true for the case of The Netherlands, however, not for other countries, please clarify.
1.2.4. 3rd paragraph, 2nd sentence: Please provide a reference, if there is an explanatory statement, why the varicella vaccination is not recommended in The Netherlands.
1.2.5. The last sentence should figure out, that the purpose is to analyse both, primary care incidence and hospital admission due to VZV related complications

1.3. Section 2.1:
1.3.1. I recommend explaining the data base in a more straightforward way. Why do you mention pharmacies in the middle of the section?
1.3.2. How is “health care center” defined? Please clarify.
1.3.3. Which data include the “information on demographics”? Age, only? Please clarify.
1.3.4. I assume that all data provided by NIVEL were in an anonymous or at least pseudonymous form. If so, please state this fact, since data protection is a quite important issue.

1.4. Section 2.3
1.4.1. Please separate more clearly between inclusion and exclusion criteria.
1.4.2. In Table 1 the ICPC codes for varicella and herpes zoster are not listed,
why that, since they are, to my understanding, inclusion criteria. What is ICPC S12?

1.4.3. Are the diagnoses on a daily exact datum? Or on a weekly frequency, only?

1.4.4. Did you include acute cases only? If yes, how did you ensure, that a case in early 2004 was not an “old” case from 2003? Did you check in general the period before diagnose, whether there was an equal diagnose, yet?

1.5. Section 2.4

1.5.1. How many experts did you contact? Please clarify

1.5.2. Did you use a systematic approach like a Delphi method? If yes please clarify.

1.5.3. I recommend to move the passage “To increase plausibility … p<0.05” in the section 2.6

1.5.4. Why did you choose verruca as plausible indication? Does verruca cause the same complications like VZV? Does verruca occur in the same age like VZV?

1.5.5. I recommend to move the passage “Varicella-related complications …more general group” right after the sentence, you mention Appendix B the in section 2.4

1.5.6. I am not able to judge, whether all indications listed in Appendix A and B, respectively are usually related or even caused by VZV. At least there are more references needed, where a connection between this complication and VZV was found.

1.5.7. Are there findings in the literature which found out, that these Indications (in Appendix A and B) occur 30 days before a VZV diagnose are related to, or caused by the VZV infection? This fact seems not clear to me.

1.5.8. Everybody, who died 30 days after a VZV diagnose was counted as VZV-related death?

1.5.9. Please provide a reference for the Taylor series linearization method

1.5.10. The hospital analysis approach seem not clear to me. You identified the cases in the way for primary care, then you analysed all referrals 21 days before and 40 days after the diagnose for VZV infection. Furthermore you analysed the related complications. Did you look for the same complications or other ones?

1.6. Section 2.5

1.6.1. The passage concerning the correction of the baseline rate via verruca, should be moved to section 2.6

1.6.2. Why did you choose verruca as plausible indication? Does verruca cause the same complications like VZV (e.g. PHN)? Does verruca occur in the same age like VZV? Please clarify this in section 2.6

1.6.3. Did you extrapolate the results by year and compute an average afterwards for the whole study period?

1.7. Section 3
1.7.1. Are the numbers presented here the numbers based on ICPC codes only? Please clarify.

1.7.2. Table 2: I recommend providing incidence rates as well.

1.7.3. I recommend presenting the absolute extrapolated numbers of varicella and HZ cases for the Netherlands.

1.8. Section 3.1.2.

1.8.1. 1st and 2nd sentences should be moved to the method section and explained more precisely

1.8.2. According to the text flow, after table 2 in section 3 comes table 6 in section 3.1.2. Table 6 should be renamed in table 3.

1.8.3. What represents in table 6 symptoms and what complications? I assume you should refer on table 3

1.8.4. Stating fever with 39.9% etc. you should refer to table 3.

1.8.5. Please state precisely which amount you refer to, complication rate or corrected rate.

1.8.6. In general I recommend to explain more specific findings, as done at the end of section 3.1.2. Repeating some numbers from the table seems to be redundant.

1.9. Section 3.1.3

1.9.1. 2nd sentence should be moved to the method section and explained more precisely

1.9.2. Please explain the negative values.

1.10. Section 3.2.1.

1.10.1. Are the incidence number based on ICPC only? Please clarify

1.11. Section 3.2.2.

1.11.1. 1st and 2nd sentences should be moved to the method section and explained more precisely

1.12. Section 3.2.3.

1.12.1. Do you see herpes zoster dermatomal rash really as a complication? It seems to be the very clinical picture of HZ causing rash.

1.12.2. If you consider immunosuppressed patients as well, please provide how you defined them in your study.

1.13. Section 3.2.4

1.13.1. 2nd sentence should be moved to the method section and explained more precisely

1.13.2. According to my comment in the method section, it seems quite unlikely that some indications you considered as complications due to HZ are really complications related to HZ.

1.14. Section 4
1.14.1. As I understand all your data are diagnosed/documneted by the GP, hence, you compared incidence data based on ICPC only and ICPC+free text

1.14.2. “97% of the hospitalizations were in healthy individuals” how did you account this?

1.14.3. Like in varicella I recommend to bring your results more into context with national and international findings.

1.14.4. I recommend separating and clustering limitations and strength better.

1.14.5. “…this limitation is not an issue” if this is the case, why are you mentioning it?

1.14.6. “verruca is, like herpes zoster and varicella, …” this sentence is way to late in the discussion, but has to be stated in the method section.

1.15. Section 5

1.15.1. There are several passages, which are stated in the discussion already. Please shorten this passage here..

1.15.2. “Moreover, almost all complications occur in previous healthy individuals” it’s not clear you to analysed that.

1.15.3. Course of life-time … at 20 at 30%…” is this a finding of your study? If not please provide a reference.

1.16. Competing interest:

1.16.1. I recommend to state, that GlaxoSmithKline is a manufacturer of a varicella vaccine.

Minor Essential Revisions

1. For review phase line and page number should be implemented in the document.

2. Section 2.4 In the sentence “The corrected rates we use” there is a “d” missing at “used”

3. Section 2.5 line 3: “…VZV or VZV related complications…” I assume it’s “varicella and HZ”

4. Section 2.5 line 2, I assume you want to refer to Appendix C rather then on Table 4.

5. Seems like in Table 2 is the label “upper respiratory tract “ is missing.

6. Section 4 2nd line: varicella “and” herpes zoster, not “en”

Discretionary Revisions

1. Since HZ incidence is increasing in people 60 plus it would be very interesting if you would analyse this population in a more detailed way like 5 year age brackets.

2. For a more precise way of estimating incidences VZV-related complications I’d recommend to perform a case-control-study rather than a cohort study.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

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

Declaration of competing interests:
I was an intern at GlaxoSmithKline from Oktober 2006 to September 2007 and an employee at Sanofi Pasteur MSD from April 2008 to May 2010.

I declare that I have no competing interests