**Statin use and the risk of herpes zoster: a nested case-control study using primary care data from the UK Clinical Research Practice Datalink**

Anthony Matthews\*, Moise Turkson\*, Harriet Forbes, Sinéad M Langan, Liam Smeeth, Krishnan Bhaskaran

Department of Non-Communicable Diseases Epidemiology

London School of Hygiene and Tropical Medicine

London UK

**Running title**

Statin use and the risk of herpes zoster

**Word Count**

Abstract: 198

Main text: 3886

Abstract

**Background**Statins are commonly prescribed worldwide and recent evidence suggests they may increase the risk of herpes zoster.

**Objective**

 To quantify the effect of statin exposure on the risk of zoster in the UK.

**Methods**A matched case-control study was conducted using data from UK primary care and hospital records. Patients >18 years with an incident diagnosis of zoster were matched to up to four controls on age, sex and general practice. Exposures were**:** ever use of a statin; daily dosage of most recent statin prescription; time since most recent statin prescription. The primary outcome was an incident diagnosis of zoster. Odds ratios were estimated from conditional logistic regression and adjusted for potential confounders.

**Results**A total of 144,959 incident cases of zoster were matched to 549,336 controls. Adjusted analysis suggested strong evidence for an increase in risk of zoster related to statin exposure (OR:1.13, 95% CI:1.11,1.15). There was also an increasing risk with increasing dose in current and recent users (p-trend<0.001), and an attenuation of excess risk in previous users as time since last exposure increased (p-trend<0.001).

**Conclusion**These findings are consistent with the hypothesis that statin therapy leads to an increase in the risk of zoster.

**Introduction**

Herpes zoster (commonly known as shingles) is caused by the reactivation of latent varicella zoster virus when specific cell mediated immunity becomes compromised. Zoster presents as a painful dermatomal vesicular rash. Healing occurs over a period of two to four weeks, and often results in scarring and permanent localised changes in skin pigmentation 1. The incidence of zoster is strongly associated with age, and 30% of cases occur in patients aged over 55 years 2. A range of conditions such as rheumatoid arthritis, imflammatory bowel disease, chronic obstructive pulmonary disorder, chronic kidney disease and depression are also associated with an increased risk of zoster 3. Postherpetic neuralgia develops (PHN) in 12% of zoster patients aged 50 years or over 1,4, and may be associated with intense pain that can last for years. A live zoster vaccine is available with efficacy in reducing the risk of zoster and postherpetic neuralgia among immunocompetent patients over 50 years old 5-7, although the vaccine is only routinely available in patients aged between 70 and 79 years in the UK 8 and recommended for patients over 60 years in the USA.

Statins are lipid lowering drugs that reduce the risk of cardiovascular disease in both primary and secondary care 9-12. In the 12 months preceding March 2008, 45.2 million statin prescriptions were dispensed in primary care in England making them the most commonly prescribed class of drugs in the UK 13. Along with being lipid lowering agents, it has been posited that statins may also modulate systemic immune responses 14. Antoniou *et al* 15 and Chen *et al* 16 recently reported a small but significantly increased risk of zoster among patients from Ontario (hazard ratio (HR): 1.13, 95% confidence interval (CI): 1.10-1.17) and Taiwan (HR: 1.21, 95% CI: 1.13, 1.29) respectively. Although the mechanisms by which statins may increase the risk of zoster are not established, it has been hypothesised that statins have immunomodulating properties, which operate by decreasing the synthesis of isoprenoid phosphates that are required for the activation of Ras-related GTPases 17, causing the impairment of T-cell activation and proliferation.

As statins are widely prescribed worldwide, any adverse effects have potentially substantial public health implications. An increased risk of zoster would not only impact on the quality of life of affected patients, but could also add to the burden on health services, given the high cost of treatment for postherpetic neuralgia 18. Hence, this study aims to quantify the effect of exposure of statins on the risk of herpes zoster in the general population of the UK.

**Methods**

A matched case-control study was conducted to quantify the effects of statin use on the risk of zoster in the UK general population.

*Data source*The data source for this study was the UK Clinical Practice Research Datalink (CPRD), which is a primary case database from general practitioners who use the Vision IT system and who have agreed at the practice level to participate 19. CPRD contains anonymised primary care data from approximately 9% of the UK population and is broadly representative of patients’ and practices’ characteristics in the UK 20. 60% of patients in the CPRD have linked data available in the Hospital Episode Statistics (HES), which has recorded hospital attendances in England since 1997.

*Selection of cases*
Zoster patients were identified from CPRD and linked HES data. All patients in the study population were 18 years or over and were under follow-up at any time between 01 January 2000 and 31 December 2011. Patients were classified as cases in the CPRD if they had a first ever zoster diagnosis recorded during the study period and at least 12 months of follow-up in CPRD prior to this first diagnosis of zoster; the 12 month restriction was intended to exclude past cases of zoster which were retrospectively recorded soon after registration at a general practice 21. In HES, incident zoster was identified according to ICD-10 (international classification of diseases, 10th revision) codes (B02, B02.0, B02.1, B02.31, B02.7, B02.8, B02.9, G53.0) that appeared in the primary diagnosis field and the index date was said to be the hospital admission date of the first episode. The earliest record of zoster was used if zoster was recorded in both HES and the CPRD for the same patient.

*Selection of controls*Up to 4 control patients were selected for each zoster case by incidence density sampling, matched on GP practice, age (within 1 year) and sex, and without reference to statin exposure status. Controls had to be registered with no history of zoster or PHN on the index date of their matched case, and have at least 12 months of prior follow-up in CPRD prior to this date. When incidence density sampling is used the odds ratio obtained from a case control study unbiasedly estimates the rate ratio in the study base.22 Matching on practice was done to minimise confounding due to differences in GP practice policies and procedures, and by factors associated with geographical area including socioeconomic status. The index date for the controls was set to that of their matched case. A control patient could also later be included as a case if they developed zoster after this date. Potential controls were assumed to be inactive with the practice and excluded if they had no contact with their GP practice at any time between six months before and 12 months after the index date.

*Exposure*
The primary exposures were ever exposure to a statin and time since last exposure to a statin. The most recent prescription of a statin before index date was initially identified and patients were then categorised into ever or never exposed to a statin.

To calculate time since last exposure, the duration of the most recent prescription before the index date was calculated from the number of tablets prescribed, combined with daily dosing instructions. When number of tablets or dosing instructions were not provided, the median number of tablets prescribed and number of tablets to be taken each day were imputed. Thirty days was then added to the prescription end date as a grace period to indicate that a patient could still be taking the same pills during this time period due to an excess of medication. Current statin use was defined as having a prescription for which the calculated duration included the index date. The number of months since statin exposure was calculated for non-current users by calculating the time between the end of the latest prescription plus the thirty day grace period, and index date. Months since exposure was categorised into current, 0-12 months since exposure, 12-36 months since exposure and >36 months since exposure.

As a secondary exposure, daily dosage of most recent statin prescription was stratified into one of three categories based on published estimates of expected reductions in LDL-cholesterol from baseline 11. These categories were low (atorvastatin <20 mg, rosuvastatin <10 mg, cerivastatin <0.3 mg, simvastatin <80 mg, fluvastatin at all doses, pravastatin at all doses, lovastatin at all doses), medium (atorvastatin 20 to <80 mg, rosuvastatin 10 to <40 mg, simvastatin ≥ 80 mg, cerivastatin 0.3 to 0.4 mg), and high (atorvastatin ≥ 80 mg, rosuvastatin ≥ 40 mg, cerivastatin ≥ 0.4 mg).

As a further exposure, duration of continuous use was calculated by retrospectively accumulating each patient’s prescriptions until there was a gap between the date of prescription and the end of the previous prescription. The date of the earliest prescription was then compared to the end date of latest prescription for non-current statin users, and date of the earliest prescription was compared to the index date for current statin users. Cumulative length of most recent exposure was categorised into less than 12 months and greater than 12 months.

**Statistical analysis**

*Primary analysis*The characteristics of the study population were described by case-control status. Conditional logistic regression was then used for analysis, so all odds ratios accounted for the matched variables of age (within 1 year), sex, practice, and calendar time. Univariate odds ratios, with 95% confidence intervals, were firstly calculated to explore the association between the risk of zoster and primary exposures of ever exposed to a statin (ever or never exposed, regardless of timing), and time since last exposure (current, 0-12 months since exposure, 12-36 months since exposure and >36 months since last statin exposure). Multivariate analyses were then carried out including the following possible zoster risk factors:3 BMI category (underweight (<18.5), normal weight (18.5-24.9), overweight (≥25-29.9), obese (≥30)), smoking status, alcohol use, cardiovascular disease (CVD), HIV, lymphoma, leukaemia, myeloma, haematopoietic stem cell transplantation, other immunosuppressive therapy, other unspecified cellular immune deficiencies, oral corticosteroids, rheumatoid arthritis, systemic lupus erythematosus, chronic obstructive pulmonary disorder (COPD), asthma, chronic kidney disease (CKD), depression, cancer, and diabetes. Details of how these risk factors were defined are outlined in appendix 1. All odds ratios were calculated using the baseline group of patients that had never been exposed to statins. A complete case analysis was done, such that individuals with missing data for BMI, smoking or alcohol were excluded; this makes the assumption that missingness of these factors is unrelated to the outcome of zoster, conditional on covariates.23

*Secondary analysis*Adjusted odds ratios, with 95% confidence intervals, were calculated to explore the association between risk of zoster and dosage of latest prescription (low, medium, high), stratified by time since last exposure. For this analysis, due to small numbers, patients in the 12-36 months and >36 months since last prescription groups were collated. The association between risk of zoster and duration of continuous use (0-12 months, >12 months), stratified by time since last exposure, was also explored.

*Effect modification*
A potentially effect modifying role of age at diagnosis (index) date was explored using the likelihood ratio test and by calculating stratum specific odds ratios in the multivariable model. For this analysis, age was treated as a binary variable, using a cut-off point of 70 years old with the rationale that these results might inform zoster vaccine policy, and the zoster vaccine is not routinely available for patients under the age of 70 in the UK.

*Sensitivity analyses*
To assess the presence of ascertainment bias, exposure to angiotensin-converting enzyme inhibitors (ACE inhibitors) was used as a negative control as they are prescribed with similar regularity and duration as statins and there is no known association between these drugs and zoster. To assess the possibility of exposure misclassification in primary analyses, we carried out an analysis where a patient was only classified as exposed to statins if they had been continuously prescribed statins for at least three months. Furthermore, to assess the short term effects of statins on the risk of zoster, we further stratified the time since last exposure analysis to include ≤3m since a statin prescription (new categories: current, ≤3m since stopping statins, >3-12m since stopping statins, >12-36m since stopping statins, >36m since stopping statins).

**Results**

*Descriptive analysis*

A total of 144 959 incident cases of zoster were identified. They were matched to 549 336 controls that were not diagnosed with zoster. Table 1 outlines the descriptive details of the cases and controls. 59.4% of cases and 61.0% of controls were female. 22.2% of cases and 20.2% controls had ever been prescribed a statin prior to index date. Overall, 14.2% and 16.1% of cases and controls respectively had at least one variable with missing data (either alcohol status, BMI category, smoking status, or a combination of all three variables).

*Ever exposed to a statin*

Univariate analysis accounting for the matched variables age, sex and GP practice presented strong evidence for an increase in risk of zoster associated with ever being exposed to a statin (OR = 1.20, 95% CI, 1.18 to 1.22). This association was attenuated when fully adjusted for potential confounders (OR: 1.13, 95% CI: 1.11, 1.15), but there was still strong evidence to suggest a modest increase in risk of zoster associated with ever being exposed to a statin.

*Time since last exposure*Table 2 and Figure 1 show unadjusted and adjusted odds ratios for the effect of statin use on the risk of developing zoster according to the timing of last exposure to statins. There was strong evidence of an attenuation of the increased risk of zoster associated with statin use as time since last prescription increased (test for trend: p<0.001).

*Dose*Table 3 and Figure 2 show unadjusted and adjusted odds ratios for the effect of the dose of the most recent statin prescription and the risk of zoster, stratified by time since last exposure. Among current statin users and recent statin users (those with a last prescription <12 months before index date), there was strong evidence for an increasing trend in risk of zoster as statin dose increased (test for trend: p<0.001 in both instances). Confidence intervals became very wide for individuals who stopped their statin therapy >12 months before the index date.

*Duration of continuous use*Results from fully adjusted analyses for duration of continuous use, stratified by time since last exposure, showed no clear evidence that the length of statin prescription modified the effect of statins on the risk of zoster. Full results are shown in appendices 2 and 3.

*Effect Modification*There was no evidence that age (treated as a binary variable indicating if a patients was over 70) modified the effect of statins on the risk of zoster (p=0.41, stratified results in appendix 4).

***Sensitivity Analyses***

*Negative control*When fully adjusted for all covariates, there was a evidence of a small increase in risk of zoster associated with ever being exposed to an ACE inhibitor in comparison to never being exposed (OR: 1.03, 95% CI: 1.01, 1.05, Table 4).

*3 months of prescription exposure*

When the statin exposed patients were required to have at least 3 months of statin prescriptions before being categorised into exposure, there was still evidence to suggest that ever being exposed to statins increased the risk of herpes zoster (OR: 1.12, 95% CI: 1.09, 1.14) when adjusted for all potential confounders.

 *Time since last exposure (short term effects)*

Appendix 5 shows unadjusted and adjusted odds ratios for the effect of statin use on the risk of developing zoster according to the timing of last exposure to statins, including a category estimating the risk in patients whose last exposure was ≤3m prior to index date. There continued to be strong evidence of an attenuation of the increased risk of zoster associated with statin use as time since last prescription increased (test for trend: p<0.001).

**Discussion**

In this large matched case-control study, statin exposure was associated with a modest increase in risk of herpes zoster (OR=1.13, 95% CI 1.11-1.15). A dose response relationship was observed and there was an attenuation of the excess risk over time among people who had stopped their statin therapy. These observations are consistent with a causal effect. An additional analysis was conducted using ACE inhibitors as a negative control exposure and we witnessed a small association, suggesting that a small proportion of the observed association between statins and zoster may be attributable to ascertainment bias or confounding by indication, but the effect size (OR=1.03) suggests that this is unlikely to explain all of the association for statins.

*Strengths and weaknesses*

All incident cases of zoster were identified in this large population-based dataset during the 11 year follow up period, hence this study was highly powered to detect small effect sizes between the use of statins and risk of zoster.

The study may be prone to misclassification of zoster as in UK primary care diagnosis of zoster is clinically based with no laboratory testing available. However, a validation study in the Netherlands found that over 90.8% of diagnosed cases in general practice had antibodies indicating recent zoster infection and suggesting that a clinical zoster diagnosis has a high positive predictive value 24.

A complete case analysis was used, which relies on the assumption the probability of these data being missing is independent of zoster risk, conditional on covariates.23 Given that only 14.2 % of cases and 16.1% of controls had missing data in smoking status, alcohol usage, or BMI category, any violation of the assumption is unlikely to importantly affect the results. Furthermore, in unadjusted analyses, effect estimates restricted to patients with no missing data were similar to estimates for the full study population.

There would be a risk of residual confounding by indication if the indication for statins also increases the risk of zoster. Statins are prescribed for both primary and secondary prevention of cardiovascular disease (CVD), which is not known to be an important risk factor for zoster. All multivariate models were adjusted for prior CVD, and this adjustment had little effect on the estimated effect of statins on zoster risk, suggesting minimal confounding. It was not possible to adjust directly for confounding by indication in primary prevention (i.e. a high risk of CVD, without an actual prior CVD diagnosis), though we did adjust for important drivers of high CVD risk including age, sex, BMI, smoking, diabetes, chronic kidney disease, cancer, and rheumatoid arthritis. However some residual confounding, for example by cholesterol level 25, cannot be ruled out.

We were unable to reliably estimate the adherence to statins of the patients included in the study, and therefore to assess the association between adherence to statin therapy and the risk of developing zoster. This is because CPRD does not collect data on drug adherence, and there was substantial missingness in the data needed to estimate prescription duration, making indirect estimation of adherence difficult.

In our negative control analysis we observed some association between ACE inhibitors use and zoster risk. The effect size was substantially smaller than in our main analysis, and the “statistical significance” should not be over-emphasised given the very high statistical power available. Nevertheless, the analysis suggests that a small part of the estimated association for statins may have been driven by non-causal factors, and there are two likely contenders: ascertainment bias, and confounding by indication. Ascertainment bias would occur if patients receiving regular preventative medications, such as statins or ACE inhibitors, were more likely to have a zoster diagnosis recorded due to the greater amount of GP contact associated with using these medications. We believe ascertainment bias is likely to have limited impact since zoster frequently presents with a very painful rash. A survey regarding immunisation practices in the United States among people aged 60 and over found that 95% of those who knew they had zoster sought care from their GP, hence the majority of zoster patients consult their GP regardless of other GP contact. In the UK context where healthcare is free at the point of delivery, we would expect that almost all patients would attend for care if they develop zoster. Residual confounding by indication may be a more likely explanation. As discussed above, we adjusted for prior CVD and for important drivers of CVD, but given the limitations of the data, some residual confounding is possible, and would likely apply similarly to both the ACE inhibitors and statins analyses, since the two drug classes have related indications.

We carried out two sensitivity analyses to assess potential biases within the analysis strategy. The first analysis consisted of requiring at least three months of statin prescriptions before defining a patient as being exposed. Imposing this restriction reduced the effect size, but not enough to change the final conclusions, which shows that the original criteria for exposure was adequate to avoid exposure misclassification. We also further stratified the time since last exposure analysis to include a category assessing the risk in patients whose last exposure was ≤3m prior to the index date. We continued to witness attenuation of the risk as time since exposure increased, with a relatively higher risk in those with the most recent prescriptions.

*Comparisons to other studies*

Although Antoniou *et al15* and Chen *et al16* undertook similar studies in Ontario and Taiwan respectively, this is the first study of its type within a UK setting. The strength of the association between risk of zoster and statin use is consistent with that found by both previous studies (1.13 (1.10, 1.17) & 1.21 (1.13, 1.29) respectively). However, neither of these studies attempted to explore the association between time since last statin and zoster infection. Our study found that zoster risk decreased as the time since last statin exposure increased, suggesting that the risk of zoster can be reduced if the patient stops statin therapy.

In this study, a dose response relationship was found in current statin users and although Antoniou *et al* classified statin dosage in the same manner as this study, they found no dose response relationship. Their study was however restricted to patients over the age of 66, whereas this study included all zoster patients and matched controls over the age of 18. Chen *et al* reported a higher risk of zoster associated with all statins prescribed at high daily dosages in comparison to those prescribed at low daily dosages. They stated that high doses of statins are prescribed to patients with high cholesterol levels, and there is limited evidence suggesting that high cholesterol levels are associated with zoster 25, which could partly explain the association found between statins and zoster.

*Conclusion*This study adds to the growing literature suggesting that statin therapy may lead to a modest increase in the risk of herpes zoster. It is clear that the preventive benefits of statin therapy are likely to outweigh the limited increase in zoster risk in many cases. However, this evidence should be taken into account by GPs when prescribing statins to those at high risk of zoster. We would also suggest that there may be an extra motivation to maximise zoster vaccine uptake among eligible patients who are also receiving a statin

**Funding**

KB is funded by a Wellcome Trust/Royal Society Sir Henry Dale fellowship. LS is funded by a Senior Wellcome Fellowship in Clinical Science. SmL is funded by a National Institute for Health Research Clinician Scientist fellowship.

**Conflicts of Interest**

None of the authors have any conflicts of interest

**Acknowledgements**

AM, MT and HF had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Contributions**

All authors contributed to the design of the study. AM and MT did the statistical analysis and wrote the first draft. All authors commented on further drafts.

**Correspondence**Krishnan BhaskaranDepartment of Non-Communicable Diseases EpidemiologyLondon School of Hygiene and Tropical Medicine**,** London UKkrishnan.bhaskaran@lshtm.ac.uk

**Alternative correspondence**Anthony Matthews
Department of Non-Communicable Diseases Epidemiology
London School of Hygiene and Tropical Medicine, London UK
anthony.matthews@lshtm.ac.uk

**What’s already known about this topic?**

* Studies in both Canada and Taiwan have recently reported small a but significantly increased risk of zoster in users of statins
* As statins are one of the most widely prescribed drugs in the UK, with around 45 million prescriptions every year, any adverse effects will have substantial public health implications

**What does this study add?**

* In this large matched case-control study, statin exposure was associated with a modest increase in the risk of herpes zoster (OR=1.13, 95% CI 1.11-1.15)
* A dose response relationship was observed, and there was an attenuation of the excess risk over time among people who had stopped their statin therapy, which indicates that the increase in risk is consistent with a causal effect
* These results suggest that there may be an extra motivation to maximise zoster vaccine uptake among eligible patients who are also receiving a statin

**References**

1 Gnann JW, Jr., Whitley RJ. Clinical practice. Herpes zoster. *The New England journal of medicine* 2002; **347**: 340-6.

2 Donahue JG, Choo PW, Manson JE *et al.* The incidence of herpes zoster. *Archives of internal medicine* 1995; **155**: 1605-9.

3 Forbes HJ, Bhaskaran K, Thomas SL *et al.* Quantification of risk factors for herpes zoster: population based case-control study. *Bmj* 2014; **348**: g2911.

4 Hope-Simpson RE. Postherpetic neuralgia. *The Journal of the Royal College of General Practitioners* 1975; **25**: 571-5.

5 Oxman MN, Levin MJ, Johnson GR *et al.* A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *The New England journal of medicine* 2005; **352**: 2271-84.

6 Langan SM, Smeeth L, Margolis DJ *et al.* Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. *PLoS medicine* 2013; **10**: e1001420.

7 Schmader KE, Levin MJ, Gnann JW, Jr. *et al.* Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2012; **54**: 922-8.

8 van Hoek AJ, Gay N, Melegaro A *et al.* Estimating the cost-effectiveness of vaccination against herpes zoster in England and Wales. *Vaccine* 2009; **27**: 1454-67.

9 Taylor F, Huffman MD, Macedo AF *et al.* Statins for the primary prevention of cardiovascular disease. *The Cochrane database of systematic reviews* 2013; **1**: CD004816.

10 Brugts JJ, Yetgin T, Hoeks SE *et al.* The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *Bmj* 2009; **338**: b2376.

11 Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *Bmj* 2003; **326**: 1423.

12 Pignone M, Phillips C, Mulrow C. Use of lipid lowering drugs for primary prevention of coronary heart disease: meta-analysis of randomised trials. *Bmj* 2000; **321**: 983-6.

13 NICE implementation uptake report: statins for the prevention of cardiovascular events. In: *NICE technology appraisal 94* (Excellence NIfHaC, ed). London: NICE. 2008.

14 Vaughan CJ, Murphy MB, Buckley BM. Statins do more than just lower cholesterol. *Lancet* 1996; **348**: 1079-82.

15 Antoniou T, Zheng H, Singh S *et al.* Statins and the risk of herpes zoster: a population-based cohort study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014; **58**: 350-6.

16 Chen HH, Lin CL, Yeh CJ *et al.* Statins can increase the risk of herpes zoster infection in Asia. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* 2015.

17 Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nature reviews. Immunology* 2006; **6**: 358-70.

18 Davies L, Cossins L, Bowsher D *et al.* The cost of treatment for post-herpetic neuralgia in the UK. *PharmacoEconomics* 1994; **6**: 142-8.

19 Herrett E, Gallagher AM, Bhaskaran K *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *International journal of epidemiology* 2015.

20 Campbell JD, D.J. Eaton, S.C. Gallagher, A.M. Williams, T.J. Is the CPRD GOLD Population Comparable to the U.K. Population? *Pharmacoepidemiology and Drug Safety* 2013; **22**: 280.

21 Lewis JD, Bilker WB, Weinstein RB *et al.* The relationship between time since registration and measured incidence rates in the General Practice Research Database. *Pharmacoepidemiol Drug Saf* 2005; **14**: 443-51.

22 Pearce N. What does the odds ratio estimate in a case-control study? *International journal of epidemiology* 1993; **22**: 1189-92.

23 White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. *Statistics in medicine* 2010; **29**: 2920-31.

24 Opstelten W, van Loon AM, Schuller M *et al.* Clinical diagnosis of herpes zoster in family practice. *Annals of family medicine* 2007; **5**: 305-9.

25 Del Pozo JL, van de Beek D, Mandrekar JN *et al.* High serum cholesterol levels are associated with herpes zoster infection after heart transplantation. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2010; **50**: 121-2.