***Increased rates of sequelae post-encephalitis in individuals attending primary care practices in the United Kingdom: a population-based retrospective cohort study***

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**Abstract**

The true extent of sequelae in encephalitis survivors relative to rates within the general population is not known. This study aimed to quantify increased risks of epilepsy, depressive disorders, anxiety disorders, psychotic disorders, bipolar disorder, cognitive problems, dementia, headache, and alcohol abuse among encephalitis cases. 2,460 exposed individuals diagnosed with incident encephalitis in the Clinical Practice Research Datalink and 47,914 unexposed individuals without a history of encephalitis were included. Multivariable Poisson regression was used to estimate adjusted rate ratios in individuals with encephalitis compared to the general population and to estimate whether the effect of these outcomes varied over time. Individuals with encephalitis had an increased risk of all investigated outcomes. The highest RR was seen for epilepsy (adjusted RR 31.9; 95% confidence interval 25.38-40.08) whereas the lowest was seen for anxiety disorders (1.46, 1.27-1.68). The second highest RRs were for particular psychiatric illnesses, including bipolar disorder (6.34, 3.34-12.04) and psychotic disorders (3.48, 2.18-5.57). The RR was highest in the first year of follow up for all outcomes except headache; this was particularly true for epilepsy (adjusted RR in first year of follow up 139.6, 90.62-215.03). This study shows that sequelae are common in survivors of encephalitis. We confirm the presence of outcomes more commonly linked to encephalitis and describe those less commonly identified as being associated with encephalitis. The results of this study have important implications for the management of encephalitis patients and for the design of tertiary prevention strategies, as many of these sequelae are treatable.

**INTRODUCTION**

Encephalitis, meaning inflammation of the brain parenchyma, is a potentially life-threatening neurological syndrome. It affects all age groups. Both direct infection of the brain and immune-mediated mechanisms can cause encephalitis; however, aetiology remains unknown in a large proportion of cases.[1] The public, clinical and scientific profiles of encephalitis have risen in recent years spurred by the recognition of emerging infections that can cause encephalitis and recognition of novel immune-mediated forms of the condition.[2-3] Research has shown that encephalitis in England is more common than previously thought with an incidence of 5-8/100,000 population, commoner than that of other neurological conditions with a higher profile and public focus such as meningococcal meningitis and motor neurone disease.[4-5]

Encephalitis is associated with high morbidity and mortality. A multicentre prospective study of ~200 English encephalitis patients reported a 12% mortality rate; a further 45% of patients had severe or moderate disabilities.[6] Survivors of encephalitis often suffer physical, cognitive, emotional, behavioural and social difficulties.[7] An outcome study in Sweden reported post-encephalitic epilepsy in 24% of survivors of herpes simplex encephalitis (HSE), while an Austrian study described a high frequency of depressive symptoms among survivors of HSE.[8-9] Long-term sequelae were assessed in a cohort of 176 French patients with all-cause encephalitis three years after hospital discharge: persisting symptoms or impaired quality of life was present in 61% of patients, most frequently concentration and behavioural disorders, emotional disorders and depression.[10]

Although it is clear from the literature that sequelae are common in survivors of encephalitis, the true extent of these sequelae relative to rates within the general population is not known. Most encephalitis outcome studies have focussed on HSE and/or are short case series (with no comparison group to quantify increased risk). There are little data on post-encephalitic morbidities in the United Kingdom (UK). It is important to assess specific long-term needs of survivors, so that tertiary prevention strategies can be designed accordingly. This study aimed to quantify increased risks of specific outcomes among encephalitis cases, including epilepsy, psychiatric disorders, cognitive problems, headache, and alcohol abuse, compared to the general population.

**METHODS**

**Study design and data sources**

A population-based retrospective cohort study was conducted using data from the Clinical Practice Research Datalink (CPRD) collected between 1988 and 2012. The CPRD has been described comprehensively by Herrett *et al*,[11] but in summary it contains anonymised primary care data for more than 4 million patients from 684 general practices (GPs) in the UK. These data, present in 10 sets of files which include clinical, referral, test and other files, contain information on demographic and lifestyle parameters, clinical events, referrals to and feedback from specialists, prescriptions and immunisation records. The data are representative of the UK populationand are subject to CPRD-imposed quality checks.[11] Data of continuous high quality considered to be suitable for research are designated ‘up-to-standard’ (UTS) data. Data in the CPRD are recorded for the most part using Read codes.[11] Numerous studies have utilised CPRD for research, and a wide range of diagnoses have been validated.[12-13]

Patient records from 58% of the contributing CPRD UK practices were provided linked to data (1997 onwards) from the Hospital Episode Statistics (HES) database. HES data include all admissions to National Health Service hospitals in England. Each record represents an episode, defined as a continuous period of hospital care under one consultant. Patients may have multiple episodes within one hospitalization. Each episode has up to 20 diagnoses, recorded using codes from the International Classification of Diseases, 10th Revision (ICD-10 codes).

**Study population**

Exposed individuals

Incident cases of encephalitis constituted the exposed group. Read codes and ICD-10 codes for encephalitis were drawn up and agreed by two of the study authors, an epidemiologist and a neurologist (JG and ND; **Appendix 1**). Data were extracted for individuals with one or more encephalitis-specific code in their CPRD records and/or in their linked HES data (in any of the 20 HES diagnostic fields) during the study period. Incident cases were defined as individuals of any age who had their first encephalitis code (in CPRD or in HES) during their UTS period and at least one year after they first registered with the practice. The latter was because individuals with prevalent or past encephalitis may have had their encephalitis recorded retrospectively in the few months after they joined the CPRD practice.[14] For incident cases with an encephalitis record present in both the CPRD and HES datasets, the earlier of the consultation or admission date was used as the date of encephalitis (index date). Individuals were excluded if they did not have at least one contact with the surgery in the two years after the index date to minimise under-ascertainment of the outcomes of interest.

Unexposed individuals

Up to 20 unexposed individuals without a history of encephalitis were selected for each exposed encephalitis patient using concurrent sampling. These individuals were matched to the encephalitis case by age (within 5 years), sex and GP and were active in the CPRD at the same time that the exposed case developed encephalitis, and with at least one year’s prior UTS data. The index date for the unexposed individual was the date of encephalitis of the matched exposed patient. Unexposed individuals were excluded if they did not have at least one contact with the surgery in the six months before to two years after the index date.

**Outcomes**

The main sequelae of interest were epilepsy; depressive disorders; anxiety disorders (including both symptom codes and diagnoses such as generalised anxiety disorder, panic disorder, post-traumatic stress disorder and obsessive compulsive disorder); psychotic disorders (including unspecified psychosis or diagnoses such as schizophrenia); bipolar disorder; cognitive problems (including memory loss, aphasia, difficulty processing information, difficulty reasoning, difficulty concentrating and learning disability); dementia (including diagnoses such as Alzheimer’s disease, presenile dementia, arteriosclerotic dementia or dementia of unspecified type); headache; and alcohol abuse (including alcoholism and alcohol misuse).

Code lists for each outcome were developed by the study authors (ND, PR, ST and JG) using Read codes and (for epilepsy) using prescription codes used in the CPRD data. Code lists for epilepsy, bipolar affective disorder, psychotic disorders and dementia were also developed using ICD-10 for use in the HES data, as patients with these conditions were considered also likely to be admitted to hospital. All code lists are available from the study authors.

To identify incident cases of the outcomes, a series of rules were applied, taking into account whether conditions were potentially recurrent and whether they could also be presenting symptoms of the encephalitis episode itself. For bipolar disorder, dementia and alcohol abuse, the first-ever code had to occur after the index date. For cognitive problems and psychotic disorders, the first-ever code had to occur ≥1 month after the index date, to allow differentiation between sequelae and presenting illness (as patients with encephalitis can present with psychosis or impaired cognition). For more common, recurrent conditions (depression and anxiety disorders), the code had to occur after the index date with no other codes in the year prior to the index date, in order to separate individuals with a “true” relapse or new diagnosis as a result of the encephalitis from those with on-going depression/anxiety. For headache (which could also be a presenting symptom of the encephalitis episode), a diagnostic code had to occur ≥1 month after the index date with no code occurring between 1 month and 1 year before the index date. Similarly, for epilepsy (given seizures are a common presenting feature of encephalitis patients), a diagnostic code had to occur ≥1 month after the index date with no code occurring >1 month before the index date; a prescription for an anti-convulsant in the post-index date period was also required. Unlike epilepsy, we did not use prescription codes in addition to a depression code as a necessary component of our depression definition, as antidepressants are often prescribed inappropriately in subthreshold or non-depression conditions and not recommended for the treatment of mild depression.[15-16]

**Data analysis**

The start of follow up for each patient was their index date. End of follow up was defined as the earliest date at which the patient developed the outcome of interest, transferred out of the practice, died, or the practice’s last data collection date. For each outcome of interest, the study population was restricted to those who were identified as at risk of having a new-onset sequela (as described in Outcomes, above). The crude rate for each outcome per 1,000 person-years (PY) was estimated in the exposed and unexposed groups. Multivariable Poisson regression was then used to estimate rate ratios (RR) for each outcome, adjusted for current age, sex, and calendar year at index date (pre-1995, 1995-2005, post-2005).

As a secondary analysis, we assessed whether the effect of the outcomes of interest varied over time. To do this, we added an interaction term for time since the index date (<1, 1-5 years, >5 years) to the multivariable model and tested using likelihood ratio tests. When there was evidence of interaction, the analyses were stratified and presented accordingly. A sensitivity analysis was also conducted in which length of follow up was adjusted for in the main model. This was to ensure that any difference in length of follow up between exposed and unexposed individuals did not affect the results.

All statistical analyses were conducted using Stata 13 (StataCorp, College Station, TX).

**RESULTS**

A total of 8,988 individuals had an encephalitis-specific code in CPRD for the relevant time period; 725 of these matched to HES. One hundred and eleven patients with a post-hepatitis A/B vaccination encephalitis code in the test or referral files only were excluded because of concern about the uncertainty of that diagnoses. A further 2,482 patients had an encephalitis-specific code in HES only. After excluding prevalent cases of encephalitis, those with no follow up during the study period and those with no contact with the surgery in the two years after the encephalitis date, 2,460 exposed incident encephalitis cases were included in the analyses (**Figure 1**). The unexposed group included a total of 47,914 individuals.

The distribution of the matching variables (demographics and calendar year at index date) was similar between the exposed and unexposed groups (**Table 1**). Almost 60% of study participants were aged between 20-65 years of age. There were slightly more females than males (53% versus 47%). Over 90% of the encephalitis diagnoses were made after 1995 in both groups. The median length of follow up was 3.5 and 4.5 years, in the exposed and unexposed groups respectively.

**Table 1. Demographics and characteristics of patients with and without encephalitis**

|  |  |  |
| --- | --- | --- |
|  | **Encephalitis (n=2,460)** | **Non-encephalitis (n=47,914)** |
| **Age (Years)** |  |  |
| *<5* | 163 (7%) | 3,242 (7%) |
| *5-19* | 345 (14%) | 6,397 (13%) |
| *20-44* | 687 (28%) | 12,635 (26%) |
| *45-65* | 695 (28%) | 14,060 (29%) |
| *>65* | 570 (23%) | 11,580 (24%) |
| *Median (IQR)* | 45 (25-63) | 47 (26-65) |
| **Sex** |  |  |
| *Male* | 1,167 (47%) | 21,922 (46%) |
| *Female* | 1,293 (53%) | 25,992 (54%) |
| **Calendar year at index date** |  |  |
| *Pre-1995* | 170 (7%) | 3,222 (7%) |
| *1995-2005* | 1,069 (43%) | 20,722 (43%) |
| *Post-2005* | 1,221 (50%) | 23,970 (50%) |
| **Median length of follow-up in years (IQR)** | 3.5 (1.3-7.9) | 4.5 (2.0-8.6) |

The crude (unadjusted) rate of all outcomes for exposed and unexposed individuals are displayed in **Table 2**. The rates ranged from 1/1,000 PY for bipolar disorder to 33.7/1,000 PY for depressive disorders in the exposed group. Rates were lower in the unexposed group, ranging from 0.1/1,000 PY for bipolar disorder to 18.3/1,000 PY for depressive disorders. Individuals with encephalitis had an increased risk of all investigated outcomes compared to those without encephalitis after adjusting for current age, sex and calendar year at index date (**Figure 2;** **Table 2**). The results remained the same when length of follow up was added to the model (data not shown). The highest RR was seen for epilepsy (RR = 31.9; 95%CI: 25.38-40.08) whereas the lowest RR was seen for anxiety disorders; however, the exposed individuals still had a 46% increased rate of anxiety disorders compared to individuals without encephalitis. The second highest RRs were for particular psychiatric illnesses, with more than six-fold rates for bipolar disorder and more than three-fold rates for psychotic disorders.

**Table 2. Adjusted and unadjusted rate ratios for outcomes**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcome** | **Number of events (%)** | **Crude rate per 1,000 person-years** **(95% CI)** | **Unadjusted RR****(95% CI)** | **Adjusted RR** **(95% CI)\*** |
|  | **Encephalitis (n=2,460)** | **Non-encephalitis (n=47,914)** | **Encephalitis** | **Non-encephalitis** |  |  |
| **Alcohol abuse** | 32 (1) | 441 (1) | 2.5 (1.8-3.6) | 1.6 (1.4-1.7) | 1.61 (1.12-2.30) | 1.60 (1.12-2.29) |
| **Cognitive problems** | 119 (5) | 1,024 (2) | 9.8 (8.2-11.7) | 3.7 (3.5-3.9) | 2.64 (2.18-3.19) | 3.07 (2.54-3.71) |
| **Dementia** | 42 (2) | 470 (1) | 4.5 (3.4-6.2) | 2.2 (2.0-2.4) | 2.08 (1.51-2.84) | 2.66 (1.94-3.65) |
| **Epilepsy** | 170 (7) | 102 (0.2) | 14.3 (12.3-16.6) | 0.5 (0.4-0.6) | 30.21 (24.06-37.92) | 31.90 (25.38-40.08) |
| **Headache** | 236 (10) | 3,144 (7) | 19.4 (17.1-22.1) | 12.0 (11.5-12.4) | 1.62 (1.42-1.85) | 1.57 (1.37-1.79) |
| **Psychiatric sequelae** |  |  |  |  |  |  |
| *Anxiety disorders* | 207 (8) | 3,258 (7) | 17.8 (15.6-20.4) | 12.3 (11.9-12.8) | 1.44 (1.25-1.66) | 1.46 (1.27-1.68) |
| *Bipolar affective disorder* | 12 (0.5) | 43 (0.1) | 1.0 (0.5-1.7) | 0.1 (0.1-0.2) | 6.18 (3.26-11.72) | 6.34 (3.34-12.04) |
| *Depressive disorders* | 367 (15) | 4,716 (10) | 33.7 (30.4-37.3) | 18.3 (17.8-18.9) | 1.84 (1.65-2.04) | 1.88 (1.69-2.09) |
| *Psychotic disorders* | 20 (1) | 143 (0.3) | 1.6 (1.0-2.5) | 0.5 (0.4-0.6) | 3.11 (1.95-4.96) | 3.48 (2.18-5.57) |

**\***Adjusted forcurrent age, sex, and calendar year at index date

There was evidence that the RRs varied by time since diagnosis/start of follow up for all outcomes except alcohol abuse and bipolar affective disorder (**Table 3**). The RR was highest in the first year of follow up for all outcomes except headache. The RR was 139.6 (95%CI: 90.62-215.03) for epilepsy in the first year, over four times higher than the overall RR of 31.9. For cognitive problems, the RR decreased after the first year but then increased again after five years of follow up. The highest RR for headache (RR 2.46 [2.05-2.96]) was seen after five years of follow up.

**Table 3. Rate ratios for outcomes by time since index date (diagnosis/start of follow up)**

|  |  |  |
| --- | --- | --- |
| **Outcome** | **Time since diagnosis/start follow-up** | **P-value\*** |
|  | *First year* | *1-5 years* | *After 5 years* |  |
| **Alcohol abuse** | 2.21 (1.02-4.83) | 1.72 (1.03-2.85) | 1.20 (0.61-2.35) | 0.52 |
| **Cognitive problems** | 5.68 (4.02-8.02) | 2.35 (1.69-3.28) | 2.67 (1.94-3.68) | <0.001 |
| **Dementia** | 4.28 (2.44-7.54) | 2.79 (1.70-4.58) | 1.72 (0.94-3.15) | 0.03 |
| **Epilepsy** | 139.59 (90.62-215.03) | 6.95 (4.06-11.90) | 3.67 (1.66-8.13) | <0.001 |
| **Headache** | 1.23 (0.88-1.73) | 1.05 (0.83-1.33) | 2.46 (2.05-2.96) | <0.001 |
| **Psychiatric sequelae** |  |  |  |  |
| *Anxiety disorders* | 2.12 (1.63-2.75) | 1.34 (1.08-1.67) | 1.21 (0.93-1.58) | <0.001 |
| *Bipolar affective disorder* | 8.89 (3.13-25.25) | 5.49 (2.07-14.57) | 4.55 (1.0-20.79) | 0.71 |
| *Depressive disorders* | 2.60 (2.16-3.14) | 1.79 (1.53-2.09) | 1.37 (1.09-1.72) | <0.001 |
| *Psychotic disorders* | 11.52 (5.39-24.62) | 2.87 (1.38-5.97) | 0.96 (0.23-3.95) | 0.005 |

\*P-value for interaction

**DISCUSSION**

This is to our knowledge the largest ever study to investigate sequelae post-encephalitis and the first to consider rates of specific sequelae amongst encephalitis survivors compared to the general population. We report an increased risk of all outcomes, including epilepsy, headache, cognitive problems and dementia, psychiatric problems and alcohol abuse, in encephalitis patients.

Epilepsy is a well-known complication of encephalitis. Post-encephalitic epilepsy and drug-resistant epilepsy was reported in 21% (31/147) and 10% (15/147) of Australian children with acute encephalitis and median follow up of seven years.[17] Our study confirms these findings: epilepsy occurred in 7% of survivors of all ages. Furthermore, we show that the rate of epilepsy in individuals with encephalitis was over 30 times higher than that of the general population, and this risk was particularly high in the first year. This has implications for patient management; survivors should be carefully monitored for seizures and epilepsy, particularly in the first year after the illness. This is especially true for patients who also initially presented with seizures, as studies have shown a further increased risk in this group.[18]

Depression has been reported to varying degrees in survivors of encephalitis.[9-10] Encephalitis clearly impacts on brain functioning and may result in depression through disruption of neurotransmitter mechanisms or pathways associated with emotional regulation. Depression can also arise as a person struggles to adjust to life after encephalitis, perhaps with a disability or a role change within the family and society.[19] We show that the rates of depression, either relapse or new-onset depression after encephalitis is almost twice as high as similar presentations in the general population. This may be an underestimate: mild depression can be difficult to distinguish from an expected reactive process to a traumatic experience like encephalitis or a functional impairment. Any communication or mobility problems also may impede ascertainment of depression. Yet clinical depression is treatable with anti-depressant drugs, psychotherapy or a combination of both and so the recognition and diagnosis of this condition is important.

Psychiatric illnesses such as psychotic and bipolar disorders and dementia have been rarely assessed in cohorts of encephalitis patients. We report higher rates of all of these outcomes in encephalitis survivors than in the general population. Patients with *N*-methyl-*D*-aspartate-receptor antibody encephalitis can present with psychosis; however, to be classified as having a psychotic disorder as an outcome in our study patients needed to have their first-ever episode of psychosis at least a month after the encephalitis diagnosis. Hence the increased RR is likely to reflect psychosis as a true sequela of encephalitis rather than just a presenting symptom. Interestingly, Scandinavian population cohort studies have shown a linear relationship between admissions with infection and diagnosis of psychosis.[20-21] Bipolar disorder has been reported, but very infrequently, as an outcome of encephalitis. A Finnish follow up study of 45 patients with acute encephalitis reported emotional instability or personality change in eight patients, including panic disorder and anxiety, bipolar affective disorder, aggressive outbursts and irritability, and depression.[22] In the same study 11% of patients had dementia.[22] There is evidence that head injuries and repeated head trauma are risk factors for amyloid brain deposition.[23] The higher rate of dementia in the first year after encephalitis was surprising. Mislabelling of cognitive problems as dementia should be considered; however, we were careful to use codes that specify dementia and we think it is unlikely that GPs would use dementia codes when describing other cognitive problems. A recent longitudinal study showed 71% and 91% with posttraumatic headache after moderate/severe and mild traumatic brain injury, respectively, one year after injury.[24]

For most outcomes in our study, the risk was highest in the first year after the encephalitis diagnosis. For headache however, the risk doubled five years after the illness compared to the first year. This might be artefact; people with encephalitis might see their general practitioner for more acute sequelae and not consider headache as important as these that soon after the acute phase of the illness. Also, patients may see their headache as an accentuation of pre-existing primary headaches rather than a new onset symptom directly related to their encephalitis and thus may delay seeking help.[25] However, it is important for these patients to seek help as headaches have a disproportionately large impact upon quality of life but they are treatable.

The strengths of our study include the large sample size, the presence of a comparison group and use of data that were collected prospectively. We chose 20 unexposed per exposed case to maximise the power of the study. The crude rate of epilepsy and depression estimated in unexposed individuals in our study are similar to those reported in the literature for the general population.[26-27] This confirms that the coding/ascertainment in CPRD appear robust enough for use in research of this nature. Also, coding for psychiatric illnesses, among others has been validated in the CPRD, further strengthening the reliability of this data source for research.[28] Primary care data were linked to hospital admissions data to maximise ascertainment of the diagnoses. A study by Beghi E *et al.* suggested that 13% of encephalitis cases do not present to hospital and may present at other places including GPs.[29] By including cases that appeared in CPRD but not HES, this study would have captured these additional cases. However, much of the CPRD-only cases were because the data were unlinked or occurred prior to 1997 (the earliest date of HES-linkage).

Possible limitations of our study also need consideration. First, the study population was restricted to those individuals who had at least one contact with the surgery in the two years after encephalitis. Thus, we may have excluded those with severe sequelae who did not remain registered with the practice; the effect estimates may be even higher. This might also explain the slightly higher female to male ratio evident in our study compared to most other studies which have shown vice versa.[30-32] Women may be more likely to survive and/or remain registered with the practice after encephalitis. Secondly, despite overall high validity of diagnoses in CPRD, encephalitis has not to our knowledge been formally validated therefore it is possible that not all cases were indeed encephalitis. Also, some of the sequelae might have been symptoms of the acute episode itself. However, this number is likely to be small because of the exclusion period used to identify outcomes and because the effect of almost all outcomes of interest persisted for more than a year after the encephalitis diagnosis. Misclassification of cognitive problems as dementia is a possibility but as discussed above we think it unlikely to be major problem. Thirdly, although our sample size was very large, we had limited power to detect whether the effect of the rarest sequelae (e.g. bipolar disorder) varied over time since diagnosis. However, we may have under-ascertained cases of bipolar disorder if a patient presented with bipolar depression (rather than mania) and was diagnosed as having depression, but then not followed up for long enough to display manic symptoms and be diagnosed correctly. Fourthly, given the nine outcomes of interest there was the potential issue of multiple testing. Therefore, the effect estimates and 95% CI need to be used to guide interpretation. Also, we will have missed people whose mental illness or alcohol use for example never resulted in contact with primary care. Finally, the length of follow up was longer for unexposed compared to exposed individuals. This means that individuals without encephalitis could have longer to develop the outcomes of interest and this could underestimate the effects, i.e. the RRs we saw for the outcomes of interest could have been even larger. However, we did adjust for length of follow up in sensitivity analyses and this made no difference to effect estimates.  Also, for most outcomes, the RR was highest in the first year after the index date. Thus any underestimation of effects might be restricted to outcomes such as headache that was only seen after five years of follow up.

In summary, this study shows that sequelae are common in survivors of encephalitis. We confirm the presence of outcomes more commonly linked to encephalitis (e.g. epilepsy and depression) and describe those less commonly identified as being associated with encephalitis (e.g. psychiatric illnesses and alcohol abuse). The results of this study have important implications for the management of encephalitis patients and for the design of tertiary prevention strategies, as many of these sequelae are treatable. Knowing these sequelae and dealing with them is thus very important for patients’ quality of life. Close follow up is crucial in the first year following the illness, but we demonstrate that sequelae can also occur many years after the initial presentation. Our results also have economic implications in terms of long-term care and loss of productivity among many working-age survivors, especially with the recently reported higher incidence rate.[4]

**CONTRIBUTORS**

All authors were involved in the design of the study. JG did the statistical analysis and wrote the first draft. All authors contributed to further drafts and approved the final manuscript. JG is the guarantor.

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**ETHICS**

This study was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare Products Regulatory Authority (ISAC\_09\_061RA2) and the Ethics Committee of the London School of Hygiene and Tropical Medicine.

**COMPETING INTERESTS**

None declared.

**DATASHARING**

No additional data available.

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**Figure 1.** Flowchart of study population

**Figure 2.** Kaplan Meier plots for outcomes of interest