S2 Table. Completed checklist to demonstrate adherence to recommended guidelines for observational studies (STROBE Statement).

	Item No.	Recommendation	Section(s)	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title	The impact and longevity of measles-associated immune suppression: a matched cohort study using data from the THIN general practice database in the United Kingdom
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract	**Objective** To test the hypothesis that measles infection increases the incidence of non-measles infectious diseases over a prolonged period of time. **Design** A population-based matched cohort study. **Data Sources** This study examined children aged 1 to 15 years in the Health Improvement Network (THIN) UK general practice medical records database. Participants included 2,228 patients diagnosed with measles between 1990 and 2014, which were matched on age, sex, GP-practice and calendar year with 19,930 children without measles. All controls had received at least one measles vaccination. Children with a history of immune-compromising conditions or with immune-suppressive treatment were excluded. **Primary outcome measures** Incidence rate ratio (IRR) of infections, anti-infective prescriptions and all-cause hospitalisations following measles in pre-determined periods using multivariate analysis to adjust for confounding variables.

				Results In children with measles, the incidence rate for non-measles infectious disease was significantly increased in each time period assessed up to 5 years post-measles: 43% in the first month (IRR: 1.43; 95%CI: 1.22 to 1.68), 22% from month one to the first year (IRR: 1.22; 95%CI: 1.14 to 1.31), 10% from year 1 to 2.5 years (IRR: 1.10; 95%CI: 1.02 to 1.19), and 15% (IRR: 1.15; 95%CI: 1.06 to 1.25) in years 2.5 to 5 years of follow-up. Children with measles were more than three times as likely to receive an anti-infective prescription in the first month and 15%-24% more likely between the first month and 5 years. The rate of hospitalization in children with measles was increased only in the month following diagnosis but not thereafter (IRR: 2.83; 95%CI: 1.72 to 4.67). **Conclusion** Following measles, children had increased rates of diagnosed infections, requiring increased prescribing of antimicrobial therapies. This population-based matched cohort study supports the hypothesis that measles has a prolonged impact on host resistance to non-measles infectious diseases.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction	The introduction of measles-containing vaccines has reduced measles incidence as well as childhood mortality. Interestingly, this reduction in childhood mortality is stronger than what would have been expected based on measles mortality in unvaccinated populations. Although measles virus is transmitted via the respiratory route, it predominantly infects immune cells and causes systemic disease. Recent studies into the mechanism of measles immune suppression, based on observations in experimentally infected non-human primates, showed that measles virus preferentially replicates in $CD150^{+}$ memory lymphocytes. It was hypothesised that viral cytotoxicity and immune-mediated clearance resulted in depletion of these cells, leading to a loss of acquired immunological memory. Consistent with this hypothesis, a subsequent ecological study using population level data from England and Wales, the United States, and Denmark, found that rates of non-measles infectious disease mortality are tightly coupled to measles incidence – with a greater mortality rate at higher recent measles incidence. Mina *et al.* measured a duration of

				measles-induced immunomodulation by assessing the association between measles incidence and childhood mortality. The results showed that measles was associated with increased mortality from other infectious diseases over a period of more than two years. However, the study was based on population-level ecological association data, and the authors did not have access to case-based data.
Objectives	3	State specific objectives, including any prespecified hypotheses	Abstract, Introduction	Objective: To test the hypothesis that children diagnosed with measles are, over a prolonged period of time, at increased risk of infectious diseases. …. to assess whether a diagnosis of measles is associated with increased frequency of non-measles infectious disease, anti-infective prescriptions, hospitalizations or death over a prolonged period of time.
Methods				
Study design	4	Present key elements of study design early in the paper	Title, Abstract, Methods	Methods: ….a matched cohort study design
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods (Data source, Study design and population, Follow-up)	For this matched-cohort study we used data from The Health Improvement Network (THIN) database. THIN is a population-based general practice registry which contains prospectively collected, anonymized longitudinal electronic patient records from over 550 General Practitioner (GP) practices across the United Kingdom (UK), capturing health care data from more than 12 million patients (about 6% of the population). Data recorded in THIN include demographic, socioeconomic, and clinical information, including chief complaint, symptoms, test results, diagnoses, prescriptions, and referrals to hospitals. The population covered has similar demographic characteristics to the national UK population, and the recording of consultations and prescriptions is comparable to national levels. Diagnoses and symptoms are recorded in Read codes, a standard terminology, maintained by the UK National Health Service Centre for Coding and Classification (NHS CCC). Information on drug prescription is recorded using British National Formulary (BNF) codes and the MULTILEX product dictionary. The specific codes used for this study were selected by a medical doctor and reviewed by a virologist, medical doctor and epidemiologist for their relevance (see S1 list for selected read codes). Information on drug prescription is recorded using British National Formulary (BNF) codes and the MULTILEX product dictionary.

				The source population consisted of all patients who had contributed longitudinal data to the database between 01 Jan 1990 to 30 Sept 2014 from the age of 6 months. The measles group consisted of children with a measles diagnosis between the ages of 1 and 15 years. The date of measles diagnosis was taken as the index date. To each child with a measles diagnosis, up to 10 children free of measles were matched. Follow-up started at the index date and continued until five years follow-up, date of transfer out the general practitioner's practice, last data collection from the general practice, the 15th birthday, or death, whichever came earliest. Four clinical outcomes were considered: infections, anti-infective prescriptions, all-cause hospitalizations and all-cause mortality. Each outcome was analysed in pre-determined periods following measles infection: within the first month; one month to 1 year; 1 year to 2.5 years; and 2.5 years to 5 years, to observe changes over time.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods (Study design and population, Outcomes)	All patients who had contributed longitudinal data to the database between 01 Jan 1990 to 30 Sept 2014 from the age of 6 months were considered eligible. The measles group consisted of children with a measles diagnosis between the ages of 1 and 15 years. Children free of measles were required to have had at least one dose of measles-containing vaccine, prior to the matched case's index date. We considered that having received at least one dose of measles-containing vaccine would provide additional certainty that children were free of measles. Patients with a history of immune-compromising conditions (e.g. HIV infection, and organ, or bone marrow transplantation), or with immune suppressive treatment prior to the index date were excluded.

				Each outcome was analysed in pre-determined periods following measles infection: within the first month; one month to 1 year; 1 year to 2.5 years; and 2.5 years to 5 years, to observe changes over time.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	Methods (Study design and population) Results	The date of measles diagnosis was taken as the index date. To each child with a measles diagnosis, up to 10 children free of measles were matched on age in years, sex, GP-practice, and calendar time in years. From the database population of 1,070,365 children aged from 1 to 15 years, we identified 2,228 eligible children with a measles diagnosis. These children were matched to 19,930 children free of measles.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods (Study design and population) Supporting information	Four clinical outcomes were considered: infections, anti-infective prescriptions, all-cause hospitalizations and all-cause mortality. We considered as potential confounders: chronic respiratory disease, cardiovascular malformation, prior exposure to childhood vaccines other than measles containing vaccines, deprivation index, health care consumption, and occurrence of each outcome of interest in the year prior to index. (please see Supporting information for specific codes used)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods , Supporting information	Patients with a history of immune-compromising conditions (e.g. HIV infection, and organ, or bone marrow transplantation), or with immune suppressive treatment prior to the index date were excluded. A child was considered diagnosed with measles if the child had a diagnostic code corresponding with measles infection. Children free of measles were required to have had at least one dose of measles-containing vaccine, prior to the matched case's index date. We considered that having received at least one dose of measles-containing vaccine would provide additional certainty that children were free of measles.

				The outcomes were defined by the relevant clinical codes for symptoms and diagnoses, or drug codes. Infections included all communicable diseases other than measles. Anti-infective prescriptions included all systemic antibiotics, anti-mycotic, antivirals and anti-parasitic medication. Infections were required to be 14 days apart to be considered a new event. Anti-infective prescriptions included all systemic antibiotics, anti-mycotic, antivirals, and anti-parasitic medication. For anti-infective prescriptions and hospitalizations, any event occurring on a different day (at least 1 day apart) was considered a new event. Potential confounders were assessed at the index date. We considered as potential confounders: chronic respiratory disease, cardiovascular malformation, prior exposure to routine childhood vaccines other than measles containing vaccines, deprivation index, health care consumption, and occurrence of each outcome of interest in the year prior to index. The Townsend deprivation score, a measure of social deprivation based on unemployment level, car ownership, home ownership, and household overcrowding levels by area, was used within a particular zip code (Townsend P, Phillimore P, Beattie A. Health and deprivation. Inequality and the North. London: Chroom Helm Ltd; 1987). Health care consumption, as a proxy for general health, was assessed by the rate of GP consultations in the year prior to the index date, (Goldstein BA, Bhavsar NA, Phelan M, Pencina MJ. Controlling for Informed Presence Bias Due to the Number of Health Encounters in an Electronic Health Record. Am J Epidemiol 2016; 184(11):847-55) and categorized using quintile cut-off points. Relevant codes were selected by a medical doctor, and reviewed by a medical doctor an epidemiologist, and a virologist for their relevance. For specific codes used for the following variables please see Supporting information: • measles, • measles vaccination, • other (childhood) vaccinations

				• infections • antibiotic prescription • all-cause hospitalisation • all-cause death • H/O immune compromising conditions • H/O chronic respiratory disease • H/O cardiovascular malformation
Bias	9	Describe any efforts to address potential sources of bias	Methods	Baseline characteristics were compared between children with measles and children free of measles using Student t-test, Mann-Whitney U-test, chi-square test, or Fisher exact test as appropriate. The differences in incidence of the outcomes between children with measles and children free of measles were analysed for each period using Poisson regression. For this analysis, matching was relaxed and the analysis was adjusted for confounding using multivariable analysis. We submitted the following confounders: history of cardiovascular malformation, history of respiratory disease, exposure to childhood vaccinations other than measles containing vaccination, age, sex, and GP consultation rate. In addition per outcome, we submitted rate of the outcome in the year prior to the index date. Absolute rates of each outcome per 1,000 person days were calculated with covariates fixed as follows: cardiovascular and respiratory history = No, Receipt of other childhood vaccines = Yes, Number of consults and events in the previous year = median, Age = 3 years, Sex = Female. To compare time to first hospitalisation, survival analysis was used. A stratified Cox proportional hazards model, stratified by matched set and adjusted for confounding variables, was applied to estimate hazard ratios comparing children with measles and children free of measles. We used backward covariate selection, using the criteria $P < 0.1$. Subsequently we verified automatically selected models using minimization of AIC.
Study size	10	Explain how the study size was arrived at	Included in protocol. Not	For a sample size calculation (https://www.statstodo.com/SSizSurvival_Pgm.php) we used an alpha of 0.05 and a power (1-beta) of 0.8. The rate of antibiotic prescription in the United Kingdom is approximately 500 prescriptions per 1,000 person-years (Schneider-Lindner V,

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<td>included in manuscript</td>
<td>Quach C, Hanley JA, Suissa S. Secular trends of antibacterial prescribing in UK paediatric primary care. J Antimicrob Chemother. 2011;66(2):424-433.). About 10-20% of children with measles experience complications during the acute phase of measles (van den Hof S, Conyn-van Spaendonck MA, van Steenbergen JE. Measles epidemic in the Netherlands, 1999-2000. J Infect Dis. 2002;186(10):1483-1486) . Based on this observation, we hypothesize that approximately 10% of all measles patients develops a level of immune amnesia that may result in a long-term increase in susceptibility to infectious disease. Because other causes of immune amnesia are unknown, we have assumed in the table below that 1-5% of non-cases develop immune amnesia from some other cause or from undiagnosed measles. Assuming that four reference persons can be identified for each index patient with measles, sample sizes as displayed below would be necessary.
<table>
<tr><th>Rate of outcome events of interest in Reference Subjects</th><th>Total Sample Size</th><th>Measles-infected subjects</th><th>Reference Subjects</th></tr>
<tr><td>1%</td><td>495</td><td>99</td><td>396</td></tr>
<tr><td>2.5%</td><td>720</td><td>144</td><td>576</td></tr>
<tr><td>5%</td><td>1670</td><td>334</td><td>1336</td></tr>
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<tr>
<td>Quantitative variables</td>
<td>11</td>
<td>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why</td>
<td>Methods (Potential confounders and effect modifiers)</td>
<td>The Townsend deprivation score, a measure of social deprivation based on unemployment level, car ownership, home ownership, and household overcrowding levels by area, was used within a particular zip code (Townsend P, Phillimore P, Beattie A. Health and deprivation. Inequality and the North. London: Chroom Helm Ltd; 1987).

Health care consumption, as a proxy for general health, was assessed by the rate of GP consultations in the year prior to the index date, (Goldstein BA, Bhavsar NA, Phelan M, Pencina MJ. Controlling for Informed Presence Bias Due to the Number of Health Encounters in an Electronic Health Record. Am J Epidemiol 2016; 184(11):847-55) and categorized using quintile cut-off points. For each outcome, the number of events in the year prior to index was calculated.</td>
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<tr>
<td>Statistical methods</td>
<td>12</td>
<td>(a) Describe all statistical methods, including those</td>
<td>Methods (Statistical analysis)</td>
<td>Baseline characteristics were compared between children with measles and children free of measles using Student t-test, Mann-Whitney U-test, chi-square test, or Fisher exact test as appropriate.</td>
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		used to control for confounding		Observed incidence rates of measles diagnosis codes as well as measles notification codes were estimated by dividing the number of cases by the number of person-years (PYs) at risk within the database stratified by calendar year, and age and were compared with expected incidence rates, derived from publicly available official statistics from the UK National Archives. (UK Government Web Archive. Measles, Epidemiological data: 1996-2013:; 2014 [updated 04 March 2014; cited 2016 09 Jun 2016]. Available from: http://webarchive.nationalarchives.gov.uk/20140505192926/http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Measles/EpidemiologicalData/) The differences in incidence of the outcomes between children with measles and children free of measles were analysed for each period using Poisson regression. For this analysis, matching was relaxed and the analysis was adjusted for confounding using multivariable analysis. We submitted the following confounders: history of cardiovascular malformation, history of respiratory disease, exposure to childhood vaccinations other than measles containing vaccination, age, sex, and GP consultation rate. In addition per outcome, we submitted rate of the outcome in the year prior to the index date. Absolute rates of each outcome per 1,000 person days were calculated with covariates fixed as follows: cardiovascular and respiratory history = No, Receipt of other childhood vaccines = Yes, Number of consults and events in the previous year = median, Age = 3 years, Sex = Female. To compare time to first hospitalisation, survival analysis was used. For this analysis, follow-up started at 30 days after the index date, to avoid including codes related to the initial measles infection. Time to first hospitalisation was described using Kaplan-Meier (K-M) estimation. A log-rank test was used to compare children with measles and children free of measles. A stratified Cox proportional hazards model, stratified by matched set and adjusted for confounding variables, was applied to estimate hazard ratios comparing children with measles and children free of measles. We used backward covariate selection, using the criteria $P < 0.1$. Subsequently we verified automatically selected models using minimization of AIC. The proportional hazards assumption was assessed by inspecting the K-M curves and formally tested with inclusion of a measles*time interaction term. We also estimated the hazard ratios for the outcomes first infection and first prescription.

		(*b*) Describe any methods used to examine subgroups and interactions	Methods	To exclude the possible effect of these unmeasured confounders, we conducted a sensitivity-analysis, stratifying the data into matched sets in which all measles cases had received, or had not received a measles-containing vaccine (i.e. non-measles group vaccinated vs measles-group vaccinated). In post-hoc analyses, we assessed the IRR of each outcome over the entire study period in vaccine adherent vs non- adherent children for each outcome using Poisson regression. We also examined the correlation of the consultation rate the year before and after the index date in measles vs. non-measles groups using linear regression.
		(*c*) Explain how missing data were addressed	Methods	Missing data was minimized by selecting a broad range of applicable codes indicating the same event. Exposed subjects without information regarding matching criteria (age, sex, practice and calendar year were excluded).
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed		Contacts were censured (follow up stopped) if they were lost to follow-up (i.e. transferred out the general practitioner's practice, data collection from the general practice stopped, or at the 15th birthday) or died whichever date came first.
		(*e*) Describe any sensitivity analyses	Methods (Sensitivity analysis)	Children who have received vaccinations may be different in their underlying health status, social background, lifestyle, health care seeking behaviour and health care utilization from those who did not receive vaccinations. To exclude the possible effect of these unmeasured confounders, we conducted a sensitivity-analysis, stratifying the data into matched sets in which all measles cases had received, or had not received a measles-containing vaccine (i.e. non-measles group vaccinated vs measles-group vaccinated). In post-hoc analyses, we assessed the IRR of each outcome over the entire study period in vaccine adherent vs non- adherent children for each outcome using Poisson regression. We

				also examined the correlation of the consultation rate the year before and after the index date in measles vs. non-measles groups using linear regression.
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig 1 Flowchart of study cohort selection	For details please see Fig 1 Flowchart of study cohort selection
		(b) Give reasons for non-participation at each stage	Results, Fig 1 Flowchart of study cohort selection	From the database population of 1,070,365 children aged from 1 to 15 years, we identified 2,228 eligible children with a measles diagnosis. These children were matched to 19,930 children free of measles. Figure 1 illustrates the composition of the study cohort. The following children were excluded (see Fig 1 Flowchart of study cohort selection); Children who experienced an exclusion criteria before cohort entrance date = 19,011 Children who were diagnosed with measles before cohort entrance date = 2,384 Children with no record of measles diagnosis or measles vaccination = 180,498 Number of children diagnosed with measles (exposed subjects) = 2,306 Number of children diagnosed with measles without information on matching criteria (i.e. age, sex, practice, and calendar year = 78 Children who were diagnosed with measles (exposed subjects) matched to children free of measles (unexposed subjects) = 2,228 Children free of measles (unexposed subjects) matched to children who were diagnosed with measles (exposed subjects; up to 10 per exposed subject) = 19,930

				Number of matched pairs= 22,158
		(c) Consider use of a flow diagram	Results	Fig 1 Flowchart of study cohort selection
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results	Table 1 Baseline characteristics of enrolled subjects
		(b) Indicate number of participants with missing data for each variable of interest	Results	See Fig 1 Flowchart of study cohort selection See Table 1 Baseline characteristics of enrolled subjects
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Results	See Table 1 Baseline characteristics of enrolled subjects The total follow-up time (days) for the exposed was 1,379.9 ± SD 595.33, with a median (IQR) of 1,826 (849 to 1,826) The total follow-up time (days) for the control group was 1,358.7 ± 611.54, with a median (IQR) of 1,826 (804 to 1,826) Median follow-up time was 5.0 person-years. There was no significant difference in follow-up time between the children with measles and the children free of measles. The percentage of children who experienced an excluding event in the follow-up period was slightly higher in the children with measles (5.61%) compared to the children free of measles (4.51%).
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Results	See Table 2. Descriptive statistics of events in enrolled measles exposed and measles-non exposed children See Fig 3 Incidence rates of non-measles infectious disease, anti-infective prescriptions, and hospitalisation

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results	See Table 3. Incidence rate ratios (IRRs) of events of interest in pre-defined time periods following measles infection
		(*b*) Report category boundaries when continuous variables were categorized	Results	Table 2. Descriptive statistics of events in enrolled measles exposed and measles-non exposed children Health care consumption, as a proxy for general health, was assessed by the rate of GP consultations in the year prior to the index date, (Goldstein BA, Bhavsar NA, Phelan M, Pencina MJ. Controlling for Informed Presence Bias Due to the Number of Health Encounters in an Electronic Health Record. Am J Epidemiol 2016; 184(11):847-55) and categorized using quintile cut-off points; 0 to 3; 4 to 7; 8 to 11; 12 to19; >19 Number of infections: 0; 1 to 2; 3 to 5; 6 to 10; >10 Number of anti-infective Rx:0; 1 to 2; 3 to 5; 6 to10; 11to 20; >20 Number of hospitalisations: 0; 1 to 2; 3 to 5; 6 to 10; >10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Results	Absolute rates of each event per 1000 person days were calculated with covariates held constant as follows: History of cardiovascular disease = No, History of respiratory disease = No, Receipt of other recommended childhood vaccinations = Yes, Number of consults in the previous year = median category (8-11), Age = Mean age (3 years), Sex = Female. These results were in alignment with the relative risks reported in the manuscript and, in the interest of conciseness, these results have not been included in the manuscript.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results (Sensitivity analysis)	Results of the sensitivity analysis were partially in agreement with findings from the main analysis. When we restricted the analysis to only those children who had received measles vaccination prior to receiving a diagnosis of measles (54.4% of all eligible children with a measles diagnosis), differences to the main analyses were not observed for infectious

				disease, or anti-infective prescriptions. However, an increased rate of hospitalisations was no longer detected in any time period. In the analysis restricted to those children who had not had a measles vaccination prior to receiving a diagnosis of measles (45.6 % of all eligible children with a measles diagnosis) the results were again in line with the main findings for infections and anti-infective prescriptions with the exception that increased risk for anti-infective prescriptions did not extend into the period 3 to 5 years following measles. Post-hoc analysis of the impact of vaccine adherence regardless of measles status revealed that vaccine non-adherent children were 42% more likely to receive an anti-infective prescription than vaccine-adherent children. There was no difference in risk of infections, or hospitalisations. Regressing post-index consults on pre-index consults and measles, or non-measles status revealed that both groups showed similar trends with the rate of consultation before index date higher than that after the index date.
Discussion				
Key results	18	Summarise key results with reference to study objectives	Discussion	We found that susceptibility to infection, as measured by rates of diagnosed infections and anti-infective prescriptions is elevated in the months to years following measles infection when compared to children free of measles. This period of increased susceptibility could be as long as five years. Children diagnosed with measles were hospitalized more frequently than children free of measles in the first month following infection as well as in the 2.5 to 5 years following infection. However, when we excluded the first month post measles, the time to first hospitalisation did not differ between the measles group and the non-measles group. This could be explained, at least in part, by the combined effect of random variation and a low number of hospitalisations. The overall trend in the increase in hospitalisations over time following infection is apparent from visual inspection of incident rate graphs. This finding warrants further investigation.

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion	A key assumption is comparability of children with measles and children free of measles. In order to ensure that the children with measles and the children free of measles were comparable we matched them on confounding factors such as age, sex, GP practice, and calendar time. We also considered including experiencing and excluding event (i.e. an immune-compromising conditions, or immune suppressive treatment) as a censoring variable but determined this was not consistent with our matching strategy – the groups were matched to be comparable at index. Nevertheless, we acknowledge that it is possible that confounding due to differences in underlying health status, social background, lifestyle, health seeking behaviour, and health care utilization between children with measles and children free of measles may have occurred. We attempted to overcome the confounding effect of underlying health status by excluding children with a history of immune-compromising conditions, and controlling for co-morbidities such as cardiovascular malformation, and respiratory disease. We adjusted for social background and lifestyle by controlling for differences in social deprivation within a particular zip code and matching on practice. Caretakers of children with measles may have had a lower threshold to visiting the GP and therefore may have had a higher likelihood of receiving a diagnosis of measles (particular during an outbreak) and may also have been diagnosed more frequently with other infectious diseases and/or may have received a prescription for anti-infectives more frequently. To investigate this we included GP consultation rate in the year prior to cohort entry as a covariate in each of our models. Because vaccinated and unvaccinated children may differ in their health seeking behaviour, or likelihood of acquiring infectious disease, we conducted a sensitivity analysis in two strata: 1) restricting to only those children who had received a measles vaccination prior to the index date, and 2) restricting to only those children who were unexposed to measles vaccination prior to the index date. Results from both sub analyses were in line with the findings from the main analysis and thus strengthen our initial conclusion. Our findings indicate that measles may have a prolonged impact on health. Additionally, we find that measles vaccination is associated with non-specific improvements in health, most likely owing to prevention of measles and its adverse immunologic sequelae. However,

				because all of our non-measles cases received vaccination, we also cannot rule out a direct benefit of vaccination to stimulate long-term heterologous immune function, as has been suggested, Blok BA, Arts RJ, van Crevel R, Benn CS, Netea MG. Trained innate immunity as underlying mechanism for the long-term, nonspecific effects of vaccines. J. Leukoc Biol 2015; 98(3):347-356. And Netea MG, Joosten LA, Latz E, Mills KH, Natoli G, Stunnenberg HG, O'Neill LA and Xavier RJ. Trained immunity: A program of innate immune memory in health and disease. Science 2016; 352(6284) in the aetiology of improved health among the non-measles cases.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion	Our findings indicate that measles may have a prolonged impact on health. Additionally, we find that measles vaccination is associated with non-specific improvements in health, most likely owing to prevention of measles and its adverse immunologic sequelae. However, because all of our non-measles cases received vaccination, we also cannot rule out a direct benefit of vaccination to stimulate long-term heterologous immune function, as has been suggested, (Blok BA, Arts RJ, van Crevel R, Benn CS, Netea MG. Trained innate immunity as underlying mechanism for the long-term, nonspecific effects of vaccines. J. Leukoc Biol 2015; 98(3):347-356. And Netea MG, Joosten LA, Latz E, Mills KH, Natoli G, Stunnenberg HG, O'Neill LA and Xavier RJ. Trained immunity: A program of innate immune memory in health and disease. Science 2016; 352(6284)) in the aetiology
Generalisability	21	Discuss the generalisability (external validity) of the study results	Methodology Discussion	The fitness of the estimated effect must be taken in the context of the GP database (THIN) and the study design. This however does not necessarily limit the extrapolation of these findings to other countries and settings.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		Not applicable

*Give information separately for cases and controls.