**Methods**

All statistical analysis was conducted with Stata 17. The outcome was mortality and the primary exposure was time following a lower respiratory tract infection (LRTi) divided into three categories: no LRTi for the duration of the study (baseline), less than 3 months from contraction (primary exposure), and greater than three months from contraction (comparator). Other independent, potentially confounding, variables measured were current age, influenza vaccination acceptance, marital status, and gender. Age was divided into 75 to 79, 80 to 84, and 85+ year bins. Vaccination acceptance was a binary variable, used as a proxy to regular vaccination. Marital status was divided into married (baseline), divorced, and single categories. The data was assessed for, but had no missing information, loss to follow-up, or blatant entry errors.

To create the primary exposure and current age variables, a lexis expansion was performed, dividing the follow-up periods by both LRTi and age categories. The data was checked for corruption following expansion; all further analysis was conducted using this expanded data.

Crude Mantel–Haenszel rate ratios (RR), 95% confidence intervals (c.i.), and chi-squared p-values were calculated for each stratum of every exposure variable to mortality. Estimates of association were also calculated for each independent variable and the primary exposure to assess for potentially confounding variables. Spearman’s test of association was conducted to assess multicollinearity. LRTi association to mortality was then individually adjusted by each independent variable by stratum of LRTi using no contraction of a LRTi as baseline.

A Poisson model was created as the intent of the study was to measure the association between predetermined time exposure groups and mortality by using the number of mortality occurrences. Each variable was individually tested for model fit against a model with just LRTi categories using likelihood ratio tests (LRTs). Effect modification (EM) was similarly tested, with LRTs comparing models with and without an interaction term between LRTi categories and each variable individually. Departure of linear trend for non-binary variables was tested after adjusting for confounding variables.

Any variables that did not act as confounding or effect modifying were dropped from the final models. Two final models were created. Both adjusted for confounding, but each had a different effect modifier. Stratified Hazard Ratios (HR), 95% c.i., and p-value estimates are reported via linear combinations of parameters (lincom) for each model separately.

**Results**

There were 868 study participants with a total of 6,266 person-years at risk. 362 (41.7%) individuals were males and 506 (58.3%) were females. 608 (70.0%) participants were married, 102 (11.8%) were divorced, and 158 (18.2%) were single. 348 (40.1%) contracted a LRTi and 368 (41.7%) refused the flu vaccination last season. The rates of mortality were as follows: no LRTi, 68.0, <= 3 months after LRTi contraction, 250.0, and > 3 months, 65.9 per 1000 person-years.

48.6% (176) of males rejected the vaccine compared to 37.9% (192) of females (p = 0.002). 36.7% (133) of males contracted a LRTi compared to 42.5% (215) of women (p = 0.09). In total, there were 438 (50.5%) deaths with no significant difference between genders (p = 0.75), but significant difference (p < 0.001) between those that did contract a LRTi (35.6%) and those that did not (60.4%).

Crude estimates provide evidence of association between LRTi at <=3 months from contraction and mortality, but not at > 3 months (Table 1). There is very weak evidence of association between gender and 80–84-year-olds with mortality, strong evidence between vaccine acceptance, 85+ year olds, and single individuals with mortality, and no evidence of association between divorced individuals and mortality (Table 1).

Age (p < 0.001), gender (p = 0.004), and vaccine acceptance (p < 0.001) are all significantly associated to LRTi categories, while marital status is not (p = 0.132). Spearman’s test of association detected no evidence of multicollinearity.

After adjusting for all variables individually, a significant association remains between LRTi at <=3 months from contraction (Table 2). There is strong evidence that gender and vaccine acceptance interact with LRTi association to mortality (Table 2), even after adjusting for age (gender p = 0.03, vaccine p < 0.001).

As marital status is not significantly associated to the primary exposure, displays no evidence of interaction, and does not change the LRTi association estimates when individually adjusted for, it was dropped from analysis.

There is no evidence of departure from a linear trend (p = 0.27) for age, but strong evidence for LRTi (p < 0.001) after adjusting for age.

The unadjusted HR for LRTi association to mortality was 3.7 (c.i. 2.4 to 5.7, p < 0.001) for <= 3 months and 1.0 (c.i. 0.8 to 1.2, p = 0.80) for > 3 months from contraction. After adjusting for age as confounding, these estimates hardly change to 3.7 (c.i. 2.3 to 5.7, p < 0.001) for <= 3 months and 0.8 (c.i. 0.7 to 1.0, p = 0.11) for > 3 months from contraction.

Amongst individuals that did not contract a LRTi, those that accepted the vaccine had 1.9 times the odds of mortality compared to individuals that rejected the vaccine (p < 0.001). At both <= 3 months and > 3 months from LRTi contraction, there was no significant difference between mortality rates of those that accepted or rejected the vaccine (Table 3). However, individuals that rejected the vaccine were 6.9 (c.i. 4.0 to 11.8, p < 0.001) times as likely to die in the three months following a LRTi compared to individuals that rejected the vaccine and did not contract a LRTi. This is in contrast to individuals that accepted the vaccine being only 1.9 (c.i. 0.8 to 4.6, p = 0.16) times as likely to die in the 3 months following a LRTi compared to individuals that accepted the vaccine and did not contract a LRTi. Additionally, at > 3 months from LRTi contraction in individuals that accepted the vaccine, there is a significant (p = 0.05) reduction of 0.7 (c.i. 0.5, 1.0) when compared to baseline individuals that did not contract a LRTi.

When stratifying by gender, there is no significant difference between male and female mortality in individuals that did not contract a LRTi, nor at > 3 months from contraction, but there is a significant (p = 0.01) 0.3 (c.i. 0.1, 0.7) times reduction in mortality in females at <= 3 months from LRTi contraction (Table 3). Males are 6.4 (c.i. 3.8 to 10.9, p < 0.001) times as likely to die at <= 3 months from LRTi contraction as baseline males. In contrast, females are 1.8 (c.i. 0.8 to 4.0, p = 0.18) times as likely to die.

**Discussion**

After adjusting for confounding, there is a 3.7 (c.i. 2.3 to 5.7, p < 0.001) times chance of mortality for care home residents aged over 75 years at <= 3 months from contracting a LRTi. Gender and influenza vaccination acceptance act as effect modifiers. There was an observed departure of linear trend for LRTi, and this is consistent with the findings that <= 3 months from LRTi there is a significant increased risk of mortality, but no such risk increase for > 3 months from LRTi.

There is a significant increase in mortality for those that accepted the vaccination and did not contract a LRTi (Table 3). However, amongst individuals that rejected the vaccine, those that contracted a LRTi were 6.9 (c.i. 4.0 to 11.8, p < 0.001) times as likely to die at <= 3 months from contraction. In comparison, amongst individuals that accepted the vaccine, those that contracted a LRTi were 1.9 (c.i. 0.8 to 4.6, p = 0.16) times as likely to die at <= 3 months from contraction. This is equivalent to a 3.6 increased chance of mortality in vaccine rejecting individuals at <= 3 months from LRTi contraction. This suggests that vaccination confers protection for individuals that contract a LRTi, but increases risk for those that do not. Participants that accepted the vaccine and contracted a LRTi were significantly less likely die at > 3 months from contraction than individuals that accepted the vaccine and did not contract a LRTi (Table 3).

Males are at increased risk (Table 3) of mortality at <= 3 months from LRTi contraction. The significant (p = 0.002) discrepancy in vaccine acceptance amongst the genders, with males being much less likely to accept vaccination, may be a contributing factor to this effect.

**Limitations**

Only the first occurrence of LRTi is recorded; there is no reinfection data.

Previous season influenza acceptance as a proxy for regular vaccination may introduce information bias if this is an inaccurate proxy measure.

As the study sample was comprised of only 75+ year olds in UK care facilities, selection bias is introduced, as there are likely differences in characteristics between elderly living in care facilities and elderly living independently.

Unmeasured confounding is a major limitation, as there are many variables such as smoking, environment, autoimmunity, and a host of other pathologies that can be associated to LRTi and mortality that were unaccounted for.

**Table 1: Crude rates, Rate ratios, 95 % c.i.s, and p-values between all variables and mortality**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Category | Rate (1000 pys) | Rate Ratio (95% c.i.) | P value |
| LRTi | None | 68.0 | 1.0 |  |
|  | <= 3 months | 250.0 | 3.7 (2.4, 5.7) | <0.001 |
|  | > 3 months | 65.9 | 1.0 (0.8, 1.2) | 0.79 |
| Gender | Male | 76.0 | 1.0 |  |
|  | Female | 66.0 | 1.2 (1.0, 1.4) | 0.14 |
| Vaccine | Refused | 54.9 | 1.0 |  |
|  | Accepted | 82.4 | 0.7 (0.5, 0.8) | <0.001 |
| Age | 75-79 | 49.1 | 1.0 |  |
|  | 80-84 | 62.0 | 1.3 (1.0, 1.7) | 0.09 |
|  | 85+ | 98.4 | 2.0 (1.5, 2.6) | <0.001 |
| Marital Status | Married | 60.9 | 1.0 |  |
|  | Divorced | 71.3 | 1.2 (0.9, 1.6) | 0.30 |
|  | Single | 116.3 | 1.9 (1.5, 2.4) | <0.001 |

Table 1: Unadjusted rates, rate ratios, 95% c.i.s, and chi-squared p-values of association between each variable stratum and mortality independently.

**Table 2: Individually adjusted HR, 95% c.i., chi2 p value, and testing effect modification**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Controlled for… | LRTi category | HR (95% c.i.) | Chi2 p-value | EM p-value |
| Age | <= 3 months | 3.6 (2.3, 5.7) | <0.001 | 0.14 |
|  | > 3 months | 0.8 (0.7, 1.1) | 0.13 | 0.51 |
| Gender | <= 3 months | 3.7 (2.4, 5.7) | <0.001 | 0.004 |
|  | > 3 months | 1.0 (0.8, 1.2) | 0.83 | 0.80 |
| Marital status | <= 3 months | 3.7 (2.4, 5.8) | <0.001 | 0.34 |
|  | > 3 months | 1.0 (0.8, 1.2) | 0.93 | 0.22 |
| Vaccine | <= 3 months | 4.2 (2.7, 6.6) | <0.001 | 0.01 |
|  | > 3 months | 1.1 (0.9, 1.4) | 0.53 | 0.01 |

Table 2: Individually adjusted HR, 95% c.i.s, chi2 p values for the association between LRTi category and mortality. Effect modification p-values are the product of approximate tests for unequal RRs

**Table 3: Final stratified Poisson regression models with interaction terms**

|  |  |  |  |
| --- | --- | --- | --- |
| **MODEL 1:** Odds of mortality by **Vaccine Acceptance** among LRTi contraction categories | | | |
|  |  | Adjusted HR (95% c.i.) | P-Value |
| No LRTi | Rejected Vaccine | 1.0 REFERENCE |  |
|  | Accepted Vaccine | 1.9 (1.5, 2.5) | <0.001 |
| <= 3 Months | Rejected Vaccine | 1.0 REFERENCE |  |
|  | Accepted Vaccine | 0.5 (0.2, 1.4) | 0.20 |
| > 3 Months | Rejected Vaccine | 1.0 REFERENCE |  |
|  | Accepted Vaccine | 1.1 (0.7, 1.6) | 0.65 |
| Main effect of LRTi in individuals that rejected the flu vaccine | No LRTi | 1.00 REFERENCE |  |
|  | <= 3 Months | 6.9 (4.0, 11.8) | <0.001 |
|  | > 3 Months | 1.3 (0.9, 1.8) | 0.20 |
| Main effect of LRTi in individuals that accepted the flu vaccine | No LRTi | 1.00 REFERENCE |  |
|  | <= 3 Months | 1.9 (0.8, 4.6) | 0.16 |
|  | > 3 Months | 0.7 (0.5, 1.0) | 0.05 |
| **MODEL 2:** Odds of mortality by **Gender** among LRTi contraction categories | | | |
| No LRTi | Male | 1.0 REFERENCE |  |
|  | Female | 1.0 (0.8, 1.2) | 0.33 |
| <= 3 Months | Male | 1.0 REFERENCE |  |
|  | Female | 0.3 (0.1, 0.7) | 0.01 |
| > 3 Months | Male | 1.0 REFERENCE |  |
|  | Female | 1.0 (0.6, 1.5) | 0.89 |
| Main effect of LRTi in males | No LRTi | 1.0 REFERENCE |  |
|  | <= 3 Months | 6.4 (3.8, 10.9) | <0.001 |
|  | > 3 Months | 0.8 (0.6, 1.2) | 0.33 |
| Main effect of LRTi in females | No LRTi | 1.0 REFERENCE |  |
|  | <= 3 Months | 1.8 (0.8, 4.0) | 0.18 |
|  | > 3 Months | 0.8 (0.6, 1.1) | 0.23 |
|  |  |  |  |

Table 3: Final stratified Poisson models assessing the relationship between LRTi and mortality, adjusted for confounding variable age. Adjusted HR, 95% c.i.s, and p-values for two separate models with integration terms.