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Authors' Affiliation:
[1]Department of Pharmacology and Toxicology, Faculty of Medicine, Umm Al Qura University, Makkah, Saudi Arabia
ORCID: 0000-0002-6453-754X
Email: smsanosi@uqu.edu.sa
[2]Department of Community Medicine, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia
ORCID: 0000-0002-5215-0049

[*]**Corresponding author**
Department of Pharmacology and Toxicology, Faculty of Medicine, Umm Al Qura University, Makkah,
Saudi Arabia
ORCID: 0000-0002-6453-754X
Email: smsanosi@uqu.edu.sa

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Do statins protect against Respiratory Tract Infection: A systematic review and meta-analysis

Safaa M Alsanosi[1*], **Asim M Alshanberi**[2]

ABSTRACT

Multiple studies have found no significant effect of the lipid-lowering drugs (statins) in reducing the risk of infections in general. However, there is a paucity of similar data on the comparative efficacy of statins on the risk of respiratory tract infections (RTIs). *Methods:* Publications of head-to-head randomized controlled trials (RCTs) of statins were retrieved from MEDLINE, EMBASE, Web of Science and Cochrane (from January 2000–December 2022). We included RCTs with at least 100 participants and with a minimum follow-up of one year. We selected the included trials, evaluated the risk of bias, and retrieved the data on RTIs. Meta-analyses were performed to summarise the pooled risk ratios (RRs) of RTIs between treatment arms. *Results:* The initial literature search identified 568 records. After duplicates were excluded, there were 318 records. Twenty-five RCTs were excluded after a full-text review of the 29 eligible studies. In the end, four RCTs with a total of 7,912 participants were included in our meta-analysis. The point estimate for the effect of statins was less than 1, however, it did not reach statistical significance in the total analysis (the pooled RR in the fixed effect model was 0.99 (95% CI: 0.94, 1.04; I2=59%; χ2 p=0.66)). *Conclusion:* Our findings showed that statins do not reduce the risk of infections (including RTIs). Additional studies are needed to gain a better knowledge about the potential effect of statins.

Keywords: Stains, Respiratory Tract, Infection

1. INTRODUCTION

Statins are a common type of lipid-lowering drug often used in patients with coronary heart diseases to lower cholesterol levels and thereby lower their mortality and morbidity (Brugts et al., 2009). They are a potent, competitive inhibitor of HMG-CoA reductase, a regulatory enzyme for cholesterol biosynthesis. Therefore, statins can decrease total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) as well as increase the level of high-density lipoprotein cholesterol (HDL-C) (Sirtori, 2014).

In addition to lowering cholesterol levels, clinical studies have shown that

statins have anti-inflammatory and immunomodulatory effects that can control the host-immune response to infections in general (such as cellulitis and sepsis) and respiratory tract infections (RTIs) in specific (such as the common cold and pneumonia) (Tleyjeh et al., 2009). Those effects are the result of a complex pathway of actions that include improvement of endothelial functions, modulation of inflammatory responses, preservation of plaque stability and the prevention of thrombus formation (Liao, 2002).

There have been several studies that evaluate the role of statins in the prevention and treatment of RTIs, such as the common cold, pneumonia and COVID-19 (Macintyre et al., 2021). Still, the absence of evidence for a beneficial effect in large, placebo-controlled trials decreases the probability of a causal effect, as reported in observational studies. On the other hand, a number of meta-analyses suggest a beneficial role of statins regarding management, risks and mortality associated with RTIs such as pneumonia and COVID-19 (Khan et al., 2013; Kow and Hasan, 2020). Still, the results of those meta-analyses included very low-quality evidence regarding observational study designs, heterogeneity and publication bias. Therefore, we conducted a systematic review and meta-analyses of randomised controlled trials (RCTs) to identify the specific effects of statins on the risk of RTIs.

2. MATERIALS AND METHODS

Literature Search

Comprehensive electronic searches of MEDLINE, EMBASE, Web of Science, and Cochrane Controlled Trials Register (CENTRAL) were conducted for the published studies from 2000 to December 2022 (Online supplement, Table S1-S4). Cross-references of all retrieved manuscripts were also checked to identify additional studies. RCTs reported in English were only included. The author (SA) conducted the initial screening (including titles and abstracts) of potentially eligible articles. Data were extracted independently by (SA and AA) using a standardised spreadsheet (Microsoft Excel 2010)

Inclusion and Exclusion Criteria

The criteria for considering and excluding studies for this review have been determined according to the Population Intervention Comparison Outcome Study (PICOS) design framework (Da-Costa-Santos et al., 2007), which groups search terms into thematic groups to select medical literature for systematic review. The standard search strategy of the lipid lowering drugs (statins), with supplementary terms, was used to identify the relevant works.

Population

(1) Definition of disease of interest: Respiratory tract infection (RTI), defined according NICE (NICE, 2008). (2) Participant characteristics: Men and women (non-pregnant women), aged 18 years and over, who had a diagnosis of RTI (as defined above), evaluated by protocol for the duration of the study. Participants could be treated with a statin before enrolment or untreated. (3) Healthcare setting: Non hospitalized patients.

Interventions and comparators

(1) Interventions: Statins included in different doses as either monotherapy or combination therapy. (2) Comparators: A placebo or another non-statin lipid lowering therapy included in different doses as monotherapy or combination therapy or non-pharmacological lifestyle approaches. (3) Co-interventions: Supplemental drugs from other classes were allowed as part of the stepped therapy.

Outcome measures

(1) Definition of outcome: RTI or RTI related mortality. (2) Measurement protocol: Reports of RTI. (3) Measurement duration: At least three months of active treatment. (4) Primary outcomes: Incidence of RTI at least one month of active treatment. (5) Secondary outcomes: The outcome of RTI infection (such as complications, severity, and mortality).

Study design

(1) Study design: Single- or multi-centre randomised controlled trials (RCTs). (2) Study sample size: RCTs that randomised at least 100 participants. (3) Study duration: RCTs that followed the participants for at least twelve months. Studies were excluded if: Participants were non-hospitalised; drugs other than the above-mentioned classes of drug were included; protocol for background drugs as well as supplemental drugs was non-pre-specified; less than 100 randomized participants or studies with a follow-up period of less than twelve months; RTI or RTI related mortality outcome was not reported.

Assessment of risk of bias within studies

The risk of bias was independently assessed by (SA and AA) for each included study, using (PRISMA) framework. Each potential source of bias was graded as high, low, or unclear.

Statistical analysis

Pooled risk ratios (RR) were calculated by choosing the fixed effects model in the Review Manager 5 software. Heterogeneity was estimated by both χ^2 test and I2 statistics. When there is statistical heterogeneity (χ^2 $p<0.05$ or I2 statistics of above 60%), sensitivity analysis will be conducted by substituting alternate decisions, and the cause of heterogeneity (methodological or clinical) will be investigated with reference to the characteristics of the studies included in the meta-analysis. Study-specific effect sizes of the standard pairwise meta-analysis model along with 95% CIs were shown in forest plots.

3. RESULTS

The initial literature search identified 568 publications. After excluding duplicates, there were 318 records. In total, 29 articles were identified as potentially eligible studies, based on abstract review. After full text review of the 29 eligible studies, 25 RCTs were excluded (two studies were on hospitalised patients, six studies randomised less than 100 participants, six studies were not RCTs and 11 studies with no outcome of interest). As in Figure 1 and Table 1, totally, 4 RCTs (ASCOT-LLA 2011, AURORA 2009, Henry 2007, Strony 2008) with a total of 7912 participants were considered appropriate for inclusion in the meta-analysis (Sever et al., 2011; Strony et al., 2008; Bone et al., 2007; Smeeth et al., 2009).

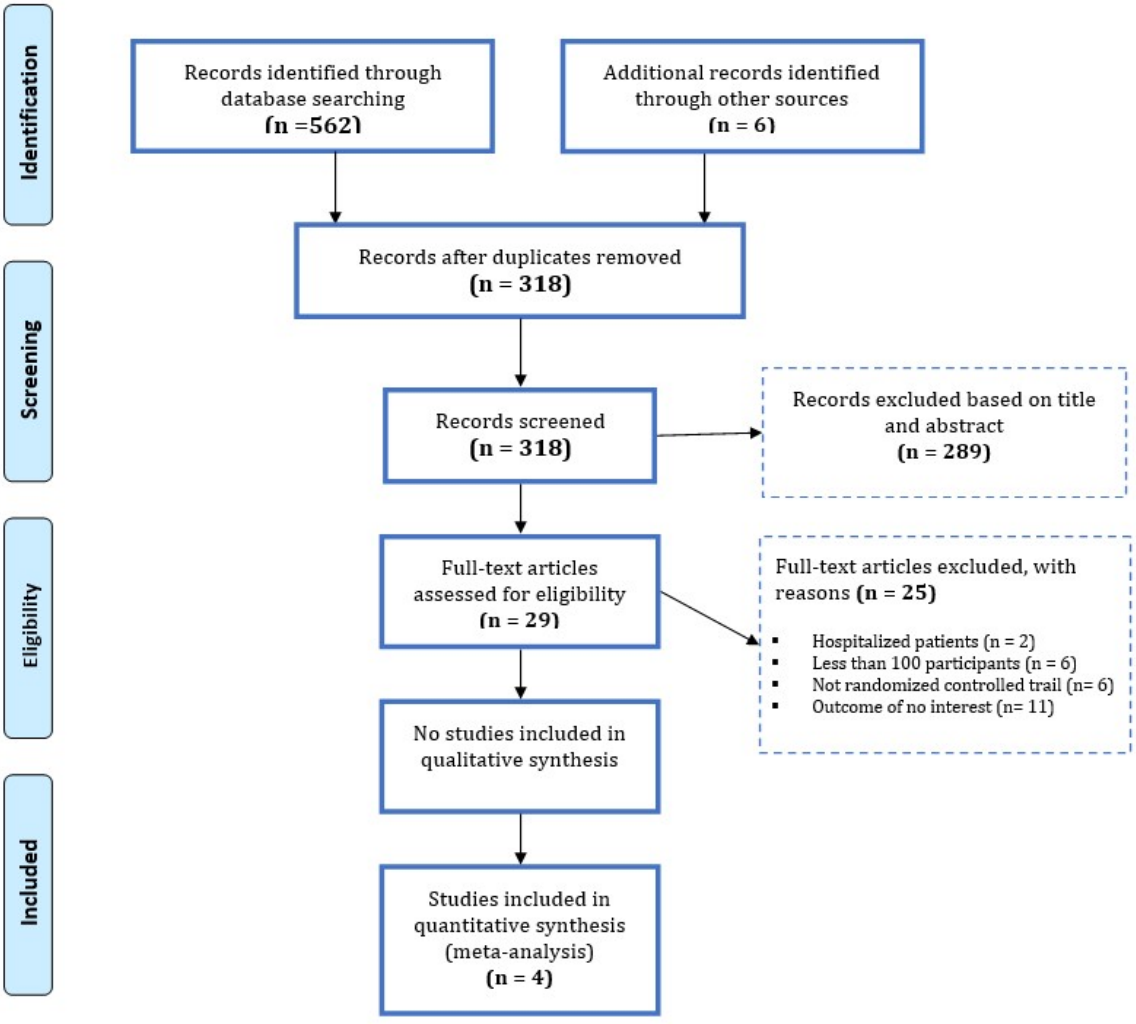

Figure 1 Flow diagram describing selection of trials for meta-analysis

Table 1 Characteristics of included RCTs (ordered by trial ID)

Study	Duration (Years)	Design	No> of Participants	Intervention	Outcomes
ASCOT-LLA [2011]	3.3	RCT	4432	Atorvastatin (10mg) vs. Placebo	RTIs, chronic obstructive pulmonary disease, acute respiratory distress
AURORA [2009]	5.6	RCT	2767	Rosuvastatin (10mg) vs. Placebo	RTIs, bronchitis, pneumonia, nasopharyngitis
Henry [2007]	1	RCT	604	Atorvastatin (10-80mg) vs. Placebo	RTIs
Strony [2008]	1	RCT	109	Simvastatin (10-80mg) vs. Ezetimibe (10mg) + Simvastatin(10-80mg)	Upper RTIs

Three of the included RCTs did not address how treatment randomization occurred (ASCOT-LLA 2011, AURORA 2009 and Strony 2008) how allocation of treatment was concealed was not mentioned in one study (Henry 2007) and therefore had an unclear risk of selection bias, as in (Figure 2). Two studies did not describe the blinding strategy with sufficient details (Henry 2007 and Strony 2008). The risk of attrition bias was high in one study (Strony 2008) whereas the risk of reporting bias was minimum in all studies.

In total, four studies were included in the meta-analysis comparing the effect of statins and other agents, as in (Figure 3). The pooled RR in the FE model was 0.99, 95% CI (0.94, 1.04) (I2=59 %; chi2 p 0.66).

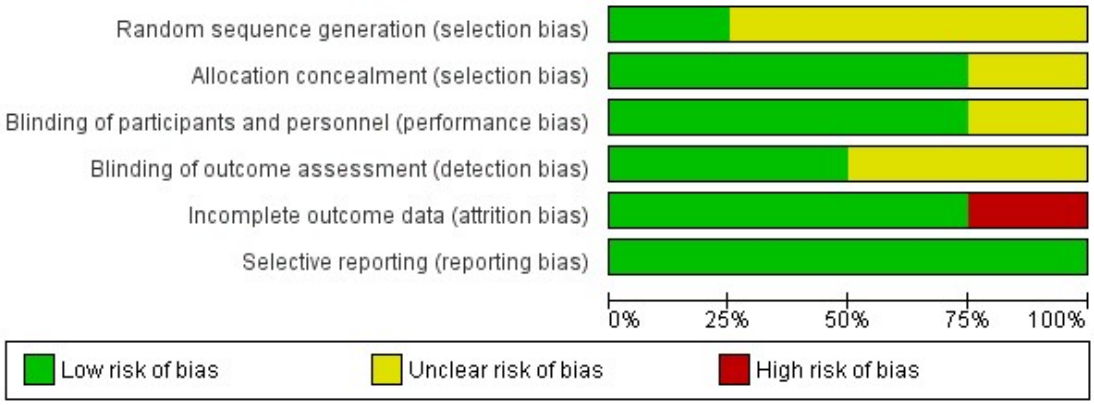

Figure 2 Risk of bias graph: Review authors' judgements about each risk of bias item, presented as % across all included studies

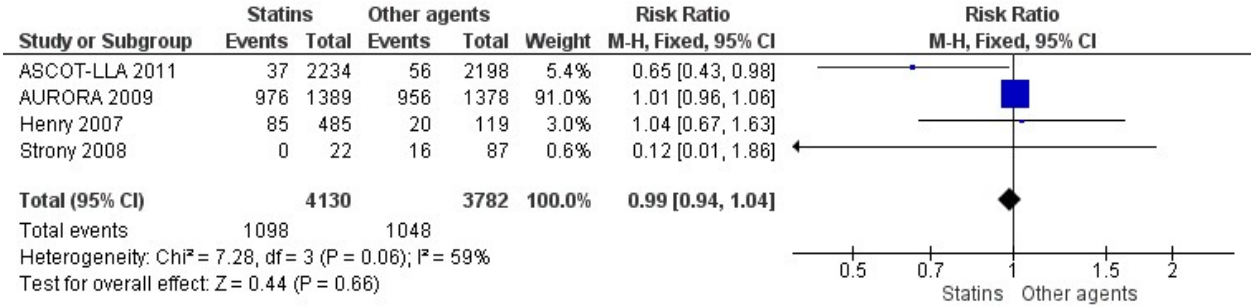

Figure 3 Forest plot of statins comparisons: RTIs outcome (FE model): Both in diagrammatic and numerical format (mmHg, 95% CI). The overall effect represents the pooled estimate of RR.

4. DISCUSSION

In this systematic review, we investigated the effect of statins on RTIs and found that the point estimate for statins was less than 1, but it did not reach statistical significance in the overall analysis. Therefore, it does not support the hypothesis that statins reduce the risk of infections (including RTIs). The protective effect of statins on the rate of infection and outcome was not supported by some studies. For instance, a meta-analysis of large RCTs investigated the effects of statins on the prevention of infections. The result indicates that the use of statins was not associated with a decrease in the risk of infection and related adverse events (including infection-related mortality) (Dublin et al., 2009).

Furthermore, a population-based cohort study conducted on statin users in the United Kingdom found that there was no strong evidence for an effect of statins on the risk of infection, and other studies reported no effect of statins in reducing the risk of pneumonia, postoperative wound infections or hospital acquired infections (Mohamed et al., 2009; Fernandez et al., 2006). By contrast, some studies reported a higher incidence of infections in statin users. A cohort study that investigated patients who received a statin for at least three months showed that there were significantly higher risks of having an infection diagnosis among statin users in comparison with nonusers. The infections included acute RTIs, pneumonia, sepsis and urinary tract infections (UTIs) (Magulick et al., 2014; Schlienger et al., 2007).

Another cohort study investigated the effect of statin use on acute RTIs and UTIs in primary care. The results showed a decreased risk for UTIs, an increased risk URTIs (Fleming et al., 2010). Still, some studies show that statins are associated with a significant decline in the risk of acute bacterial infections, including RTIs, pneumonia and post-operative infections (Nassaji et al., 2015; Van-De-Garde et al., 2006; Kayani et al., 2013).

However, in those studies, either the risk reduction was particularly strong in the subgroup of patients, or the eligible patient number was relatively small. Moreover, the effects of some confounding factors, such as the severity of infection and duration of infection, were not considered, and participants on statins received better health assistance, which can induce confounding effects. Our study has several strengths. We conducted a comprehensive review covering all potential and accessible sources of information and carefully evaluated the quality and risk of bias in all the individual studies included in the meta-analysis. However, a limitation is the small number of RCTs included in our study.

5. CONCLUSIONS

The findings of our systematic review and meta-analysis do not show that statins decrease the risk of infections (including RTIs). However, to gain a greater understanding of the potential effect of statins, further meta-analyses or RCTs with large samples are required to define better the association between statin use and the risk and outcome of RTIs.

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

Supplementary Materials

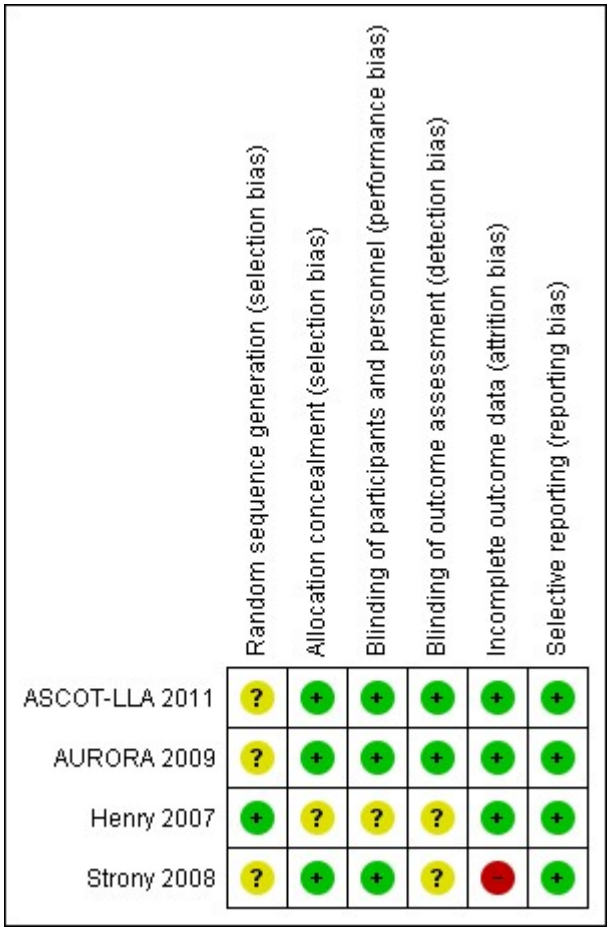

Figure S1 Risk of bias graph: Presented as % across all included studies

Table S1 Search strategy for MEDLINE (OVID): 2000- December 2022

#	Searches
1	HMG-CoA reductase inhibitors.mp.
2	Anticholesteremic agents.mp.
3	Statin.ab.
4	Simvastatin.mp.
5	Rosuvastatin.mp.
6	Pravastatin.mp.
7	Atorvastatin.mp.
8	Fluvastatin.mp.
9	Cerivastatin.mp.
10	Pitavastatin.mp.
11	Lovastatin.mp.
12	Or/1-11
13	Infection/
14	(Respiratory adj2 infection).tw.
15	Infect$.tw.
16	Or/13-15
17	12 and 16
18	Randomized controlled trial.pt.
19	Randomized.ab.

20	Placebo.tw.
21	Drug therapy.tw.
22	Randomly.ab.
23	Trial.ab.
24	Or/18-23
25	Animals/ not (humans/ and animals/)
26	24 not 25
27	17 and 26
	Limit 27 to (yr="2000-2022" and "all adult (19 plus years)")

"mp" indicates multi-purpose search terms; "Ab" indicates all searchable words from the abstract;
"/" indicates that it is a Medical Subject Heading (MeSH) term;
"adj" plus a number between any two terms returns records that contain both terms within the specified number of words from each other;
"tw" indicates that the term is a text word meaning the title and abstract;
"Pt" indicates publication types, such as reviews, clinical trials, directories and letters.

Table S2 Search strategy for EMBASE (OVID): 2000- December 2022

#	Searches
1	HMG-CoA reductase inhibitors.mp.
2	Anticholesteremic agents.mp.
3	Statin.ab.
4	Simvastatin.mp.
5	Rosuvastatin.mp.
6	Pravastatin.mp.
7	Atorvastatin.mp.
8	Fluvastatin.mp.
9	Cerivastatin.mp.
10	Pitavastatin.mp.
11	Lovastatin.mp.
12	Or/1-11
13	Infection/
14	(Respiratory adj2 infection).tw.
15	Infect$.tw.
16	Or/13-15
17	12 and 16
18	Randomized controlled trial.pt.
19	Crossover procedure.mp.
20	Double-blind procedure.mp.
21	(Doubl$ adj blind$).tw.
22	(Clin$ adj25 trial$).tw.
23	Placebo$.tw.
24	Random$.tw.
25	(Meta?analys$ or systematic review$).tw.
26	(Crossover$ or cross-over$).tw.
27	Or/18-26
28	(Animal$ not human$).sh,hw.
29	27 not 28
30	12 and 17 and 29
	Limit 30 to (yr="2000 - 2022" and adult <18 to 64 years>)

"mp" indicates multi-purpose search terms; "Ab" indicates all searchable words from the abstract;
"/" indicates that it is a Medical Subject Heading (MeSH) term; "tw" indicates that the term is a text word meaning the title and abstract;
"adj" plus a number between any two terms returns records that contain both terms within the specified number of words from each other;
"Pt" indicates publication types, such as reviews, clinical trials, directories and letters; "$" indicates all possible suffix variations of the root word;

"?" indicates the retrieval of documents with British and American word variants; "sh" indicates all searchable words in the subject heading field; "hw" indicates all searchable words in the heading word field.

Table S3 Search strategy for CENTRAL: 2000- December 2022

#	Searches
1	HMG-CoA reductase inhibitors.tw.
2	Anticholesteremic agents.mp.
3	Statin.tw.
4	Simvastatin.tw.
5	Rosuvastatin.tw.
6	Pravastatin.tw.
7	Atorvastatin.tw.
8	Fluvastatin.tw.
9	Cerivastatin.tw.
10	Pitavastatin.tw.
11	Lovastatin.tw.
12	#11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
13	Infection.tw.
14	(Respiratory adj2 infection).tw.
15	Infect$.tw.
16	#15 OR #14 OR #13
17	#12 and #16
	Limit to Publication Year from 2000 to 2022

"tw" indicates that the term is a text word, meaning the title and abstract; "mp" indicates multi-purpose search terms; "adj" plus a number between any two terms returns records that contain both terms within the specified number of words from each other; "$" indicates all possible suffix variations of the root word.

Table S4 Search strategy for Web of Science: 2000-December 2022

#	Searches
1	TS="HMG-CoA reductase inhibitors"
2	TS="anticholesteremic agents"
3	TS="Statin"
4	TS="Simvastatin"
5	TS="Rosuvastatin"
6	TS="Pravastatin"
7	TS="Atorvastatin"
8	TS="Fluvastatin "
9	TS="Cerivastatin"
10	TS="Pitavastatin"
11	TS=" Lovastatin"
12	#11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
13	TS=" infection"
14	TS=(*respiratory infection*)
15	#13 OR #14
16	#12 and #15
17	TI="randomized controlled trial"
18	TI="controlled clinical trial"
19	TS="Randomized"
20	TS="Placebo"
21	TI="drug therapy"

22	TS="Randomly"
23	TI="Trial"
24	#23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17
25	TS=(animals/ not (humans/ and animals/))
26	#24 NOT #25
27	#16 and #26
	Limit to Publication Year from 2000 to 2022

"TS" indicates all searchable words in the topic subject; "TI" indicates all searchable words in the title;
"*" indicates any group of characters, including no character; "" indicates a search for the exact phrase appearing between the quotation marks.

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