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# Pre-habilitation with intratympanic gentamicin in vestibular schwannomas: a systematic review

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**Review Article**

Prof Kontorinis takes responsibility for the integrity of the content of the paper

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## Abstract

**Objective.** To assess whether pre-habilitation with intratympanic gentamicin can accelerate vestibular compensation following vestibular schwannoma resection.

**Methods.** Seventeen studies were retrieved from the databases Medline, PubMed, Frontiers, Cochrane Library, Cambridge Core and ScienceDirect. Eight of the 17 studies met our criteria; the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used. Heterogeneity, risk of bias and effect on post-operative recovery were assessed.

**Results.** Four of the eight studies showed a statistically positive effect of pre-habilitation with gentamicin on the post-operative recovery process; the remainder also reported benefits, although not statistically significant. No study reported negative effects. Limitations were linked mostly to the limited number of enrolled patients and the outcome assessment methods.

**Conclusion.** Fifty per cent of the studies found a statistically positive effect of pre-habilitation with gentamicin prior to vestibular schwannoma resection. While the results are promising, due to the limited numbers further prospective studies are required to strengthen the evidence.

## Introduction

Vestibular schwannomas are benign tumours that develop from the sheath of the vestibulocochlear nerve.[1] Most vestibular schwannomas are unilateral, so-called sporadic, and mostly present with unilateral or asymmetric sudden or progressive sensorineural hearing loss, with or without persistent unilateral tinnitus. Problems with balance or other compression phenomena could be present depending on the size of the tumour and whether there is compression of cranial nerves or brainstem structures.[1,2] While tumour measurement methods can vary, the size of the tumour can be classified as small (less than 1.5 cm), medium (1.5–2.5 cm), large (2.5–4.0 cm) and giant (more than 4.0 cm).[3] There can be differences in the management of patients with vestibular schwannomas due to local preferences and available resources; however, generally, for larger tumours, microsurgery is the preferred choice of treatment, with translabyrinthine and retrosigmoid approaches used for vestibular schwannomas with intracranial extension.[3] Surgical removal of vestibular schwannomas usually causes acute vestibular symptoms.[4] These acute vestibular symptoms are a key factor in the post-operative recovery process; thus, targeting them is important in order to speed up vestibular compensation and post-operative recovery.

Previous studies have shown that pre-operative intratympanic gentamicin application can result in a substantial reduction in peripheral vestibular function in all semicircular canals.[5] Should intratympanic gentamicin be applied pre-operatively, it could prevent sudden loss of peripheral vestibular function and speed up vestibular compensation after vestibular schwannoma resection.[5] Based on the above concept and published works, some centres have used intratympanic gentamicin pre-operatively to improve recovery times post-operatively.

Despite the presence of some studies, there has been no systematic assessment of the level of evidence behind such a relatively new intervention. On these grounds, this systematic review aimed to perform an analysis of studies assessing the effect of pre-habilitation with intratympanic gentamicin on patients' recovery following vestibular schwannoma resection.

## Materials and methods

### *Search strategy and research question*

We performed a systematic review with the research question being whether pre-operative intratympanic gentamicin injections improve the post-operative recovery following vestibular schwannoma resection. We used the databases Medline, PubMed, Frontiers, Cochrane Library, Cambridge Core and ScienceDirect to identify published studies on

the pre-operative use of intratympanic gentamicin in patients with vestibular schwannomas. We used the key words 'intratympanic gentamicin', 'vestibular schwannoma', 'preoperative', 'prehabilitation' and 'vestibular compensation'. The local Library Network facilitated a comprehensive literature search.

Our methodology was adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') 2020 guideline for systematic reviews.[6] We used the 'PICO' (P-Population, I-Intervention, C-Control or Comparison, O-Outcome) framework to review the different components of the studies included, as mentioned in the Cochrane Handbook for Systematic Reviews.[7]

### Eligibility criteria

We initially retrieved 17 studies. Overall, nine of these met the inclusion versus exclusion criteria (Figure 1).

Our inclusion criteria were studies that: (1) are clinical; (2) were published within the last 20 years; (3) were published in English or German language; and (4) involved the use of intratympanic gentamicin pre-operatively in vestibular schwannoma patients prior to vestibular schwannoma resection.

We excluded: (1) case reports; (2) conference abstracts; (3) studies that were published more than 20 years ago because pre-habilitation is a relatively recently described concept; and (4) studies with patients with vestibular schwannomas treated with pre-operative intratympanic gentamicin assessing factors not related to their post-operative recovery.

Using our inclusion and exclusion criteria, one potential study, by Tjernström *et al.*,[5] was excluded. While the objective in that study was to evaluate vestibular and auditory function after pre-habilitation with gentamicin in vestibular schwannoma patients, it reported the effect on function before patients underwent surgery, not after. Thus, a total of eight studies were included in this review.

### Collected data

We collected the following listed data: (1) geographic origin and year of the study; (2) the presence of a control group; (3) level of evidence; (4) number of enrolled patients; (5) intratympanic gentamicin regimen and injection procedure; (6) outcome measures of effect of intratympanic gentamicin on recovery; (7) size of vestibular schwannoma (dimensions or Koos classification); (8) surgical approach; and (9) side effects from intratympanic gentamicin.

### Data analysis and risk of bias

Due to the small number of patients, we did not compose the data; instead, we used a qualitative analysis. In order to ensure validity and reliability of the retrospective studies included in this paper, a tool was used to assess risk of bias in case–control studies (Appendix 1).[8] We accepted the heterogeneity of the included studies as a limitation, given the overall absence of control trials and limited number of enrolled patients.

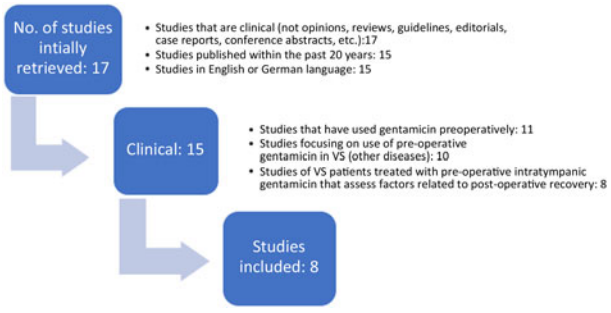


**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') flowchart. VS = vestibular schwannoma

## Results

A total of eight studies were included and qualitatively analysed (Figure 1). The findings and characteristics of the included studies have been summarised (Tables 1–3) to allow for overview and comparison.[9–16]

### Study origin and tumour-related factors

All the included studies originate from European countries; interestingly, there were none from the USA or Asia, areas that traditionally contribute significantly to the literature in this specific field. This distribution of the included studies probably highlights geographic differences in practice. The available studies have relatively few patients, ranging from 4 to 39 patients in each group (examined and control groups). The age distribution did not significantly vary across the different studies. All patients selected in the studies had a vestibular schwannoma with a tumour size ranging from grade II to grade IV (based on the Koos grading system for vestibular schwannomas), with linear measurements being the ones reported. Tumours were resected mainly via the retrosigmoid or translabyrinthine approach. In the study by Fellmann *et al.*,[9] 10 per cent of patients underwent a transtemporal approach; in the work by Magnusson *et al.*,[10] the resection approach was not specified (Table 1). The level of evidence was predominantly level IV (Table 1).[17]

### Outcome measures and assessment methods

In terms of intervention and/or exposure, a sufficient dose of gentamicin to cause vestibular ablation was given to the patients in the gentamicin group, while the patients in the control group were managed without pre-operative gentamicin application. The Video Head Impulse Test and/or caloric testing were used to monitor vestibular function in patients. In certain studies, additional testing was carried out, which included the subjective visual vertical measurement, posturography and the Activities-specific Balance Confidence scale in Hrubá *et al.*,[11] as well as the subjective visual vertical scale, optokinetic testing and Dizziness Handicap Inventory, General Behaviour Inventory and Glasgow Health Status Inventory in Balatkova *et al.*[12] and Čada *et al.*[14] Tjernström *et al.*[13,15] and Magnusson *et al.*[10] also used posturography parameters (vibratory perturbation) in addition to the Video Head Impulse Test and caloric testing.

### Control group

The patients for both the control group and the gentamicin group were selected based on similar inclusion and/or exclusion criteria in all studies, although the screening tests used varied. In general, among other criteria that each study had developed, inclusion criteria for the control group included patients with serviceable hearing, as defined by the studies, a large tumour size that was considered unsafe to wait for several months for surgery to take place, and lack of consent for intratympanic gentamicin. Most studies also had criteria based on vestibular function and postural performance prior to surgery,

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**Table 1.** Included studies, with demographics, approach and vestibular schwannoma size

| Study | Year | Level of evidence[17] | Country | Surgical approach | Tumour size (mean ± SD, or range; mm) |
|---|---|---|---|---|---|
| Fellmann *et al.*[9] | 2021 | IV | Switzerland | Translabyrinthine 38%, Retrosigmoid 52%, Transtemporal 10% | 20.2 ± 9.4 |
| Amiraraghi *et al.*[16] | 2019 | IV | UK | Translabyrinthine | 26.7 ± 4.5 |
| Hrubá *et al.*[11] | 2019 | IV | Czech Republic | Retrosigmoid | 22.1 ± 10.6 |
| Balatkova *et al.*[12] | 2019 | IV | Czech Republic | Retrosigmoid | 15.0–50.0 |
| Tjernström *et al.*[13] | 2018 | IV | Sweden | Translabyrinthine 44%, Retrosigmoid 56% | 17.3 ± 9.0 |
| Čada *et al.*[14] | 2016 | IV | Czech Republic | Retrosigmoid | 10.0–40.0 |
| Tjernström *et al.*[15] | 2009 | IV | Sweden | Translabyrinthine | 5.0–40.0 |
| Magnusson *et al.*[10] | 2008 | IIIb | Sweden | Not specified | 4.5–25.0 |

SD = standard deviation

**Table 2.** Participant numbers and gentamicin regimens

| | Gentamicin group | | Control group | | | | |
|---|---|---|---|---|---|---|---|
| Study | Participants (*n*) | Age (mean (± SD); years) | Participants (*n*) | Age (mean (± SD); years) | Gentamicin dosage (total (concentration)) | Gentamicin regimen | Use of vHIT? |
| Fellmann *et al.*[9] | 29 | 49.6 ± 11.5 | 39 | 49.6 ± 11.5 | 0.3 ml (40 mg/ml) | 1 intratympanic injection, followed by ≥1 injection after 2 weeks until vestibular hypofunction detected via vHIT | Yes |
| Amiraraghi *et al.*[16] | 4 | 36.3 ± 12.0 | 4 | 40.7 ± 11.2 | 0.6–0.8 ml (40 mg/ml) | 2–3 intratympanic injections, 1-week interval between doses | Yes |
| Hrubá *et al.*[11] | 16 | 49.1 ± 14.4 | 36 | 47.3 ± 12.8 | 0.3–0.6 ml (40 mg/ml) | 3 intratympanic injections in 1 day with 2-hour interval between doses | Yes |
| Balatkova *et al.*[12] | 11 | 48.4 ± 11.3 | 21 | 44.1 ± 11.4 | 0.5–1.0 ml (40 mg/ml) | 3 intratympanic injections, 2–3 weeks interval between doses | Yes |
| Tjernström *et al.*[13] | 20 | 51.4 ± 13.6 | 24 | 50.0 ± 12.4 | 1.0–2.0 ml (30 mg/ml) | 2–4 intratympanic injections, interval not specified | Yes |
| Čada *et al.*[14] | 10 | 50.0 | 10 | 50.0 | 1.0 ml (40 mg/ml) | 3 intratympanic injections, 2 days interval between doses | Yes |
| Tjernström *et al.*[15] | 6 | 50.0 | 35 | 51.3 | 0.3–0.4 ml | 4 intratympanic injection, 2 days interval between doses | Yes |
| Magnusson *et al.*[10] | 12 | 50.0 | – | – | 1.2 ml (30 mg/ml) | 4 intratympanic injections, 2-day interval between doses | Yes |

vHIT = Video Head Impulse Test; SD = standard deviation

and all of the studies performed tests to assess vestibular function such as the Video Head Impulse Test. However, one of the studies, Čada *et al.*,[14] did not have criteria based on vestibular function or postural performance prior to surgery. Another study, by Magnusson *et al.*,[10] did not have a control group, which potentially limits the ability to confirm that the study results are due to manipulation of independent variables and not extraneous variables (Table 2).

## Outcomes

None of the studies reported any clinically significant side effects. With regard to whether there is an effect of prehabilitation with gentamicin in vestibular schwannoma patients on the post-operative recovery process, four of the studies showed a statistically significant positive effect, while the remaining four studies showed better outcomes for the intratympanic gentamicin group, but without a statistically significant difference. In the latter four studies, a degree of benefit was reported, as some of the patients had shorter in-patient stay or exhibited fewer symptoms of postural impairment, albeit the results are not statistically significant, which might have been due to the small number of enrolled patients. In addition, three of the studies used posturography parameters to demonstrate a long-term positive effect (Table 3). One of the studies, Magnusson *et al.*,[10] demonstrated an additional benefit of the use of intratympanic gentamicin in vestibular schwannoma patients with tumours compromising the cerebellum but with preserved vestibular function (Table 3).

## Risk of bias

We assessed the risk of bias using five domains (see Appendix 1 for additional details): (1) can we be confident in the

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**Table 3.** Outcome measures and side effects

| Study | Main outcome measures | Results | Reported side effects |
|---|---|---|---|
| Fellmann *et al.*[9] | DHI, postural stability using functional gait assessment | Vestibular pre-habilitation with gentamicin has no effect on postural stability & dizziness during walking in VS patients | – |
| Amiraraghi *et al.*[16] | Effect on contralateral labyrinth using vHIT, length of in-patient stay | Pre-operative intratympanic gentamicin improves recovery following VS resection | Patients who received gentamicin had mild fibrosis in middle ear, not clinically significant |
| Hrubá *et al.*[11] | vHIT, caloric testing, subjective visual vertical scale, posturography parameters, Activities-specific Balance Confidence scale | No statistically significant difference in vestibular compensation process in early post-operative period between group pre-habilitated with intratympanic gentamicin & control group | – |
| Balatkova *et al.*[12] | GBI, Glasgow Health Status Inventory, DHI, visual symptoms & optokinetic sensation via specific questionnaire developed by research team (pre-operative) & routine electronystagmography (post-operative), Zung self-rating depression scale, generalised anxiety disorder assessment questionnaires | No statistically significant differences between both groups in terms of quality of life; pre-treatment with gentamicin helped lower anxiety levels in patients, which improved general post-operative status; pre-treated patients were less sensitive to optokinetic stimulation than control group | Pre-habilitated patients less sensitive to visual & optokinetic stimulation |
| Tjernström *et al.*[13] | vHIT, caloric testing, posturography parameters (vibratory perturbation) | By separating sensory loss (with intratympanic gentamicin) from intracranial surgical trauma, postural control system benefited from better short-term (adaptation) & long-term (habituation) recovery | – |
| Čada *et al.*[14] | GBI, Glasgow Health Status Inventory, DHI, visual symptoms & optokinetic sensation via specific questionnaire developed by research team | Vestibular pre-habituation with pre-operative gentamicin ablation of vestibular function does not significantly improve quality of life after VS resection | – |
| Tjernström *et al.*[15] | vHIT, caloric testing, posturography parameters (vibratory perturbation) | Gentamicin group demonstrated significantly less postural sway post-surgery compared to control group | – |
| Magnusson *et al.*[10] | vHIT, caloric testing, vestibular-evoked myogenic potential, subjective visual vertical scale, posturography parameters, pure tone & speech audiometry | There was loss of caloric reaction & impulses, all subjects were vestibular compensated before surgery & no patient complained of post-operative dizziness or vertigo | – |

DHI = Dizziness Handicap Inventory; VS = vestibular schwannoma; vHIT = Video Head Impulse Test; GBI = Glasgow Benefit Inventory

assessment of exposure to gentamicin?; (2) can we be confident that cases had developed the outcome of interest (i.e. that intratympanic gentamicin had an effect on recovery) and controls had not?; (3) were the cases (those patients who were exposed to gentamicin and developed the outcome of interest) properly selected?; (4) were the controls (those patients exposed to gentamicin who did not develop outcome of interest) properly selected?; and (5) were cases and controls matched according to important prognostic variables, or was statistical adjustment carried out for those variables?

With respect to the assessment of exposure to gentamicin and outcome measures, we identified an increased risk of bias if evidence of exposure and outcome of interest were acquired by subjective methods, as was the case in many papers. However, reasonable steps had been taken across the included studies to provide independent validation of the results. In the selected studies, objective tools of measurement used included diagnostic tests such as the Video Head Impulse Test and caloric stimulation for the neuro-otologic examination of the vestibulo-ocular reflex. Therefore, although some studies used subjective measurements, they combined more than one test to validate their results. This reduced the level of bias. There was, however, as noted above, significant heterogeneity.

With respect to patient selection, the studies investigated specific groups; any control groups were appropriately matched. In one of the studies, Balatkova *et al.*,[12] the selection was not strictly random due to ethical concerns. Patients with serviceable hearing were preferentially assigned to the control group, and those with large tumours that surpassed Koos grade 4 (defined by a large tumour with brainstem and cranial nerve displacement) had the choice to willingly undergo gentamicin treatment because the probability of hearing preservation for them was low. In addition, the sample sizes for all the studies are relatively small, which can possibly result in a type II error and limit the randomisation process. As such, there was probably a low associated risk of bias.

With regard to the risk of bias linked to the matching of cases and controls according to important prognostic variables, there was statistical adjustment carried out for important prognostic variables across all the studies included in this review; hence, in this domain the risk of bias was low for all the studies.

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## Discussion

### Main outcome

This review systematically assessed the effect of vestibular pre-habilitation with intratympanic gentamicin in vestibular schwannoma patients post resection. Eight studies met the criteria and were included. While the outcome measures varied, the results in four of the eight studies show that there is a statistically better post-operative performance in the gentamicin group than in the control group. The remaining four studies still demonstrated better outcomes but without reaching the level of statistical significance. As such, the studies showed that there is either a beneficial effect (four studies with statistical and four without statistical significance), or no negative effect without associated side effects.

It has been well demonstrated that a major post-operative concern in vestibular schwannomas is post-operative vestibular symptoms, which incapacitate the patient by prolonging recovery times. However, by employing vestibular ablation with intratympanic gentamicin prior to resection, it is possible to avoid this. We recognise that stronger evidence, conducting studies with larger cohorts and standardised outcome measures, is still required; however, the existing evidence, at least partially, supports intratympanic gentamicin as pre-habilitation in patients with vestibular schwannomas undergoing resection. Given the number and the limitations of the existing studies, this outcome should be implemented in clinical practice with caution.

### Special considerations

There are a few potential limitations relating to the risk of bias in the included studies. The outcome measures used in the included studies involved a variety of questionnaires and subjective tests. As the studies concerned used other questionnaires and tests to supplement the outcome measures listed earlier, the risk of bias is mitigated. In terms of selection bias, the sample sizes for all the studies are relatively small, which can have an effect on the observed outcomes. However, a moderating factor is that there was statistical adjustment carried out for important prognostic variables across all the studies included in this review. Additionally, it is worth accepting that the number of vestibular schwannoma resections is relatively limited; thus, obtaining large numbers, involving control groups, can be challenging.

As seen in Table 1, most of the studies utilised retrosigmoid and/or translabyrinthine approaches for vestibular schwannoma patients, except Fellmann *et al.*[9] in which 10 per cent of patients underwent a transtemporal approach. None of the studies focused specifically on differences between the approaches and response to gentamicin pre-habilitation. However, given the documented outcomes, it appears that intratympanic gentamicin can help post-operative recovery regardless of the approach. While one could argue the potential hearing-preserving character of a retrosigmoid approach and any potential cochleotoxicity of gentamicin, this was not really assessed. Additionally, the effect of gentamicin on hearing was not specifically addressed in the included studies, because this was not the main focus of any of the papers that we examined.

Overall, we found that the included papers offered a good overview of how patients recover following vestibular schwannoma resection with and without pre-operative intratympanic gentamicin. All studies demonstrated good post-operative outcomes, with the main difference being speed of recovery, which was faster for the gentamicin group. There was significant heterogeneity of the outcome measures; thus, the term 'better post-operative outcome' cannot be interpreted uniformly throughout the available literature. Essentially, while most patients will recover eventually, the ones treated with pre-habilitation are more likely to recover sooner. This has been linked primarily to the gradual effect of gentamicin in ablating vestibular function, compared to the sudden effect of surgery through labyrinthectomy or vestibular nerve resection or a combination of both.[5,9,10,18] The work by Amiraraghi *et al.*[16] showed, using Video Head Impulse Tests, the milder effect of surgery on the contralateral side in patients from the gentamicin group, providing a reasonable explanation of the positive effect of pre-habilitation.

### Limitations of evidence

Most limitations were related to the study design and primarily to the small size of the included cohorts. This was addressed through the risk of bias assessment. A few aspects of clinical significance are worth noting. The gentamicin regimen is not homogeneous across the studies (Table 2). The concentrations, number of injections and intervals between each dose vary significantly. In addition, one of the studies, Tjernström *et al.*,[13] did not specify an interval between injections or injections and surgery. This is not necessarily a limitation because no adverse effects were reported and the goal was to ablate vestibular function, which the studies did successfully, regardless of the regimen used. Many studies primarily used the Video Head Impulse Test as a screening tool and to assess vestibular function after administration of gentamicin injections; it was also used following surgery in the study by Amiraraghi *et al.*[16] Four studies additionally used caloric testing, which has the limitation of assessing only the lateral semicircular canal; the Video Head Impulse Test has been shown to be more capable than caloric testing in assessing the function of each of the six canals individually and has been used more frequently since 2009.[19] However, as the studies used both caloric stimulation and the Video Head Impulse Test, the accuracy of the results was not compromised.

### Implications of results for practice, policy and future research

Four of the eight studies demonstrated clinically significant statistical differences between the gentamicin group and the control group. The remaining studies showed, although not statistically significant, evident benefits post-operatively when vestibular schwannoma patients were pre-habilitated with intratympanic gentamicin. Three of the eight studies even indicate long-term benefits using vibratory posturography data. While we accept the limitations of the existing studies, it appears that ablation of vestibular function achieves compensation before surgery and speeds up recovery. There is some risk of hearing loss with intratympanic gentamicin injections,[20] but this risk must be weighed against the benefit of recovery. This is especially so if patients already have significant hearing loss or are undergoing translabyrinthine surgical resection of their vestibular schwannomas, because the gentamicin would not add any additional morbidity, particularly if no hearing-preservation surgery is being considered. Nevertheless, if hearing-preserving vestibular schwannoma resection is considered, the risk of hearing loss due to

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gentamicin should be thoroughly considered; this could potentially be a contra-indication for pre-habilitation with gentamicin.

## Conclusion

Given the published evidence, the results support the rationale of pre-habilitating patients with vestibular schwannomas with intratympanic gentamicin prior to surgical resection. This conclusion should be adopted with caution in clinical practice because more prospective studies and larger sample sizes are needed to support it and strengthen the developing evidence.

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**Competing interests.** None declared

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## Appendix 1. Risk of bias assessment tool

| Study (reference) | Definitely yes (low risk of bias) | Probably yes | Probably no | Definitely no (high risk of bias) |
|---|---|---|---|---|
| Can we be confident in the assessment of gentamicin exposure? | | | | |
| Fellmann *et al.*[9] | ☐ | ☐ | ☐ | ☐ |
| Amiraraghi *et al.*[16] | ☐ | ☐ | ☐ | ☐ |
| Hrubá *et al.*[11] | ☐ | ☐ | ☐ | ☐ |
| Balatkova *et al.*[12] | ☐ | ☒ | ☐ | ☐ |
| Tjernström *et al.*[13] | ☒ | ☐ | ☐ | ☐ |
| Čada *et al.*[14] | ☐ | ☒ | ☐ | ☐ |
| Tjernström *et al.*[15] | ☒ | ☐ | ☐ | ☐ |
| Magnusson *et al.*[10] | ☒ | ☐ | ☐ | ☐ |
| Can we be confident that cases had developed outcome of interest* & controls had not? | | | | |
| Fellmann *et al.*[9] | ☒ | ☐ | ☐ | ☐ |
| Amiraraghi *et al.*[16] | ☒ | ☐ | ☐ | ☐ |
| Hrubá *et al.*[11] | ☒ | ☐ | ☐ | ☐ |
| Balatkova *et al.*[12] | ☒ | ☐ | ☐ | ☐ |
| Tjernström *et al.*[13] | ☒ | ☐ | ☐ | ☐ |
| Čada *et al.*[14] | ☒ | ☐ | ☐ | ☐ |
| Tjernström *et al.*[15] | ☒ | ☐ | ☐ | ☐ |
| Magnusson *et al.*[10] | ☒ | ☐ | ☐ | ☐ |
| Were the cases (those who were exposed & developed outcome of interest) properly selected? | | | | |
| Fellmann *et al.*[9] | ☒ | ☐ | ☐ | ☐ |
| Amiraraghi *et al.*[16] | ☒ | ☐ | ☐ | ☐ |
| Hrubá *et al.*[11] | ☒ | ☐ | ☐ | ☐ |
| Balatkova *et al.*[12] | ☐ | ☒ | ☐ | ☐ |
| Tjernström *et al.*[13] | ☒ | ☐ | ☐ | ☐ |
| Čada *et al.*[14] | ☐ | ☒ | ☐ | ☐ |
| Tjernström *et al.*[15] | ☒ | ☐ | ☐ | ☐ |
| Magnusson *et al.*[10] | ☒ | ☐ | ☐ | ☐ |
| Were the controls (those who were exposed & did not develop outcome of interest) properly selected? | | | | |
| Fellmann *et al.*[9] | ☒ | ☐ | ☐ | ☐ |
| Amiraraghi *et al.*[16] | ☒ | ☐ | ☐ | ☐ |
| Hrubá *et al.*[11] | ☒ | ☐ | ☐ | ☐ |
| Balatkova *et al.*[12] | ☐ | ☒ | ☐ | ☐ |
| Tjernström *et al.*[13] | ☒ | ☐ | ☐ | ☐ |
| Čada *et al.*[14] | ☐ | ☒ | ☐ | ☐ |
| Tjernström *et al.*[15] | ☒ | ☐ | ☐ | ☐ |
| Magnusson *et al.*[10] | NA | NA | NA | NA |
| Were cases & controls matched according to important prognostic variables or was statistical adjustment carried out for those variables? | | | | |
| Fellmann *et al.*[9] | ☒ | ☐ | ☐ | ☐ |
| Amiraraghi *et al.*[16] | ☒ | ☐ | ☐ | ☐ |
| Hrubá *et al.*[11] | ☒ | ☐ | ☐ | ☐ |
| Balatkova *et al.*[12] | ☒ | ☐ | ☐ | ☐ |
| Tjernström *et al.*[13] | ☒ | ☐ | ☐ | ☐ |
| Čada *et al.*[14] | ☒ | ☐ | ☐ | ☐ |
| Tjernström *et al.*[15] | ☒ | ☐ | ☐ | ☐ |
| Magnusson *et al.*[10] | ☐ | ☒ | ☐ | ☐ |

*Refers to effect of intratympanic gentamicin on recovery

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