"This is the peer reviewed version of the following article: **Vollset, Knut Wiik; Krontveit, Randi Ingebjørg; Jansen, Peder A; Finstad, Bengt; Barlaup, Bjørn Torgeir; Skilbrei, Ove Tommy; Krkošek, Martin; Romundstad, Pål Richard; Aunsmo, Arnfinn; Jensen, Arne Johan; Dohoo, Ian.** Impacts of parasites on marine survival of Atlantic salmon: a meta-analysis. *Fish and Fisheries* 2016 ;17:3;714-730, ***which has been published in final form at*** http://onlinelibrary.wiley.com/doi/10.1111/faf.12141/epdf.

Impacts of parasites on marine survival of Atlantic salmon: a meta-analysis

Knut Wiik Vollset[1*], Randi Ingebjørg Krontveit[2a], Peder Jansen[3], Bengt Finstad[4], Bjørn Torgeir Barlaup[1], Ove Tommy Skilbrei[5], Martin Krkošek[6], Pål Romunstad [7], Arnfinn Aunsmo[2b], Arne J. Jensen [4], and Ian Dohoo[8]

[1] Uni Research,[2]Norwegian University of Life Sciences ([a] Current working address: [a]Norwegian Medicines Agency, [b] AquaGen AS), [3]Norwegian Veterinary Institute, [4]Norwegian Institute for Nature Research, [5]Institute of Marine Research, [6] University of Toronto, [7] Norwegian University of Science and Technology, [8] University of Prince Edward Island

*Corresponding author, email: knut.vollset@uni.no, tlf: 55584723

Running title: Parasites and marine survival of salmon

Abstract

Parasites can, in theory, have large impacts on the survival of fish populations. One method to evaluate such impacts on anadromous species is to apply manipulative field experiments in which parallel groups of anti-parasitically treated and non-treated fish are simultaneously released and then subsequently recaptured as returning adults. A systematic review and meta-analysis on all such Norwegian studies on *Salmo salar* provided a dataset for the time period 1996 to 2011 on 118 release groups comprising 657 624 fish released and 3 989 recaptured. The overall risk ratio (RR), calculated as the probability of being recaptured in the treated group divided by the probability of being recaptured in the control group, was estimated to be 1.18 (95 % CI: 1.07-1.30). The effect varied strongly between groups, quantified by Higgins measure of heterogeneity (I^2 = 40.1%). Over 70% of this heterogeneity could be explained by the release location, time period and baseline survival. The most important predictor variable was baseline survival. In groups with low recapture in the control group (low baseline survival), the effect of treatment was high (RR = 1.7), while in groups with high recapture in the control group (high baseline survival), there was no effect of treatment (RR ~ 1.00). The most prevalent parasite in the region affected by the drugs administered was *Lepeophtheirus salmonis*. Hence, the meta-analysis supports the hypothesis that anti-parasitic treatment protects *S. salar* smolts from *L. salmonis* during outward migration. However, the effect of treatment was not consistent, but was evidently strongly modulated by other risk factors. The results suggest that the population level effects of parasites cannot be estimated independently of other factors affecting the marine survival of *Salmo salar*.

Keywords: salmon louse, emamectin benzoate, substance EX, *Lepeophtheirus salmonis*, fish farming, parasite

Contents

Introduction

Domestication of marine fishes is relatively new compared to terrestrial food production, and the recent expansion in marine farming now provides 15.6 % of the global fish supply (FAO 2014). Aquaculture growth reflects the large and growing market demand for seafood and the stagnation of wild fishery landings. In recent years, the debate regarding the role of farmed marine fish as hosts and reservoirs for diseases and parasites has spurred the debate about the sustainability of net pen farming and its effects on wild fish populations (Costello, 2006, Torrissen et al., 2013). At the core of this debate is the role of farmed Atlantic salmon (*Salmo salar*, Salmonidae) as hosts of parasites – typically the ectoparasitic copepod salmon lice (*Lepeophtheirus salmonis*, Caligidae) – and the possible effects of this role on wild salmonids. Farmed Atlantic salmon are mostly produced in open-net pen installations in coastal areas within the natural range of wild salmonids. These locations often overlap with the migration paths of young wild salmon smolts migrating to the sea, and the main concern is therefore whether the additional farm-generated production of diseases and parasites, such as salmon lice, will inflict additional mortality during this vulnerable life stage (Krkošek et al., 2013).

The role of parasites in regulating host populations has been the subject of a longstanding debate (Anderson and May, 1978, May and Anderson, 1978). While estimating the effects of parasites on populations is technically possible, in reality there are several difficulties related to quantifying such effects. This difficulty is perhaps especially the case for marine fish populations, where survival is highly variable and strongly linked to variations in environmental conditions during early life stages (Cushing, 1975, Hjort, 1914). For example, the recruitment of different stock complexes of Atlantic salmon has been shown to vary with different climate indices (e.g. Atlantic Multidecadal Oscillation (Friedland et al., 2014)). The sublethal effects of salmon lice likely interact with other components of survival, such as competition or predation risk (Godwin et al., 2015), making it difficult to use observational data to separate the role of the parasite from other effects. One alternative approach is to study the effects of parasites on host fitness in a controlled laboratory environment (Bjoern and Finstad, 1998, Finstad et al., 2000, Wells et al., 2006, Wagner et al., 2008), but extrapolating results from these studies to natural systems is often questioned. Another method is to perform experimental field trials with releases of control groups and groups treated with an anti-parasitic agent and compare the subsequent recaptures of adults in the two groups (randomized control trials, RCT). Such field experiments have become increasingly popular with researchers studying salmon lice and Atlantic salmon in recent years, as they are believed to give unequivocal results regarding the relative role of the parasites on the marine survival of salmon (Gargan et al., 2012, Jackson et al., 2013, Skilbrei et al., 2013, Vollset et al., 2014, Krkošek et al., 2013).

Since the 1990s in Norway, numerous trials have been conducted to evaluate the effect of anti-parasitic treatments applied to hatchery produced salmon smolts on survival to recruitment after one, two or more years at sea. In each trial, smolts have been tagged and assigned to one of two groups: control or anti-parasitic treatment. Two different anti-parasitic treatments have been used, emamectin benzoate (with marketing authorization, oral administration via feed or as intra-peritoneal injection) and Substance Ex (without marketing authorization, chitin synthesis inhibitor, topical bath treatment –(Skilbrei et al., 2015)). Because individual fish in each trial are tagged, recovery programs for recruits can then identify these fish and calculate the difference in survival between the control and treatment groups. The hypothesis has been that long-acting anti-parasitic treatment would protect salmon smolts predominantly from salmon lice during outward migration, increasing post-smolt survival and, consequently, the number of returning adult salmon.

Studies conducted in Norway, Ireland, and Scotland (Gargan et al., 2012, Jackson et al., 2013, Skilbrei et al., 2013, Vollset et al., 2014, Krkošek et al., 2013) indicate that treatment of salmon smolts prior to release into the river or the fjord generally increases the number of recaptured returning adult fish. However, treatment effects have been highly variable. A positive effect of anti-parasitic treatment on the length and weight of Atlantic salmon has also been reported (Skilbrei et al., 2013, Skilbrei and Wennevik, 2006). Recently, Vollset et al. (2014) also demonstrated that treated salmon return earlier than untreated salmon indicating a sublethal effect of salmon lice on surviving individuals. Some of the Norwegian trials have been conducted over a decade in the same river (Skilbrei et al., 2013, Vollset et al., 2014). However, in several trials, the number of recaptured fish has been low, and the power to detect differences has also been low.

A meta-analysis is a statistical method in which data derived from a systematic review are weighted (in proportion to the amount of evidence provided by the study) when computing an overall estimate of the effect (Borenstein et al., 2010). The objectives of the present study were to perform a meta-analysis of all available material, both published and non-published, on anti-parasitic treatment trials in Norway to obtain an overall estimate of the effect of treatment on the survival of Atlantic salmon across studies and to explore the role of study- and trial-level covariates on the treatment effect size by the use of subgroup analyses and meta-regression. A secondary goal was to evaluate whether trial-level variation in treatment effect (i.e., heterogeneity) was related to variations in sea lice infection pressure from salmon farms situated along the migration routes of the smolts. The systematic review was therefore limited to Norway because of the availability of counts of salmon lice from fish farms and thus the ability to evaluate the contribution of salmon lice from fish farms. The systematic review resulted in a dataset of 118 release groups in the time period 1996 to 2011, comprising 657 624 fish released and 3 989 recaptured.

Materials and methods

Systematic review

A systematic review of all published and non-published studies using anti-parasitic agents on release groups of Atlantic salmon smolts was conducted to identify Norwegian studies that could be defined as randomized control trials (RCTs). All details of the systematic review are provided in the supplemental material (S1), including a list of variables extracted from all of the studies. In short, the review consisted of (1) a workshop with experts within the field of salmon lice ecology, epidemiology and biostatistics, (2) a standardized literature search of relevant databases (Aquatic Sciences and Fisheries Abstracts and CAB abstracts) and (3) a letter to all potential research institutions inquiring whether any non-published data were missed. A list of all the trials identified with the corresponding data is given in the supplementary data (S2).

Salmon lice exposure from fish farms

As part of our analysis, we sought to evaluate whether trial-level variation in treatment effect was related to variation in sea lice infection pressure from salmon farms situated along the migration routes of the smolts. In Norway, it is mandatory to monitor and report monthly data on salmon lice abundance, total number of fish on the farms and mean fish weight. From 2002 to 2011, farmers were instructed to report the highest abundance of sea lice encountered during each month (Jansen et al., 2012). These data are available from 2002 onwards and formed the basis for infection pressure modeling along the Norwegian coast in different months. Infection pressure estimates for the given month were calculated by multiplying adult female lice abundance by the reported number of fish per farm. To derive an expression for the intensity at all locations along the coast, lice numbers were interpolated by kernel density functions in ArcGIS, Spatial analyst. Two variants of the kernel density interpolations were undertaken, using search radii of 50 and 200 km. No data exists that can inform the exact migratory route of smolt from the different release points. Acoustic studies has shown that smolt migrate relative fast outwards toward saline waters upon release (Thorstad et al., 2012). Therefore, the shortest path to the open sea was estimated and used as an objective method to define the migratory route. Furthermore, statistics for this pathway intersecting the grid-layers on adult female lice were extracted. These statistics consisted of the accumulated sum of grid-cells intersected, the mean or the maximum of grid cells. The method is described in greater detail in (Jansen et al., 2012). These data were then used as a proxy for the exposure of migrating salmon smolts to salmon lice of farm origin. The method was also used to estimate temperature exposure along the migration route based on measurements at the same fish farms.

Statistical analysis

Meta-analysis was selected as the most appropriate method for combining evidence from the numerous trials which had been conducted. A summary of the analyses conducted is provided here, with details of all steps provided below.

- Outcomes (treatment effects) to be evaluated were identified
- Random effects meta-analyses using standard procedures were carried out
- Heterogeneity (variance in estimates of treatment effect across studies) was quantified
- Standard meta-regression techniques were used to evaluate factors which might have contributed to the variation in results across studies. This was initially done by evaluating unconditional associations (one factor at a time) and subsequently by building a multivariable model (simultaneous evaluation of multiple factors)
- One factor – baseline survival (proportion of fish recaptured in the non-treated fish) - deserved special attention because standard meta-regression techniques would provide a biased estimate of the effect of this factor. An alternative approach to evaluation of this factor was adopted, first replicating the multivariable model developed in the proceeding

step and subsequently evaluating it on its own in order to provide a graphic representation of its effect.

- Factors that influenced baseline survival were evaluated using standard univariable and multivariable regression techniques
- The potential impact of publication bias, information bias and selection bias were all evaluated
- The impact of treatment in terms of additional recaptures attributable to treatment was computed as an attributable fraction (AF)

Several outcomes of interest were computed. First, the number of released fish and the number of recaptured fish were used to calculate the risk ratio (RR) of treatment in each release group. Risk ratio (RR) is defined as the probability of being recaptured in the treated group divided by the probability of being recaptured in the control group. In addition, weight and length data were available from a smaller subset of releases from Vosso, Dale, Matre, Eira, Årdal, Imsa and Halselv. For these releases, the mean weights and lengths of the treatment and control fish were computed to obtain an estimate of the weighted mean difference in weight and length by treatment group. Descriptive statistics for all variables were computed, and a histogram of the RR was generated.

Each of the three main outcomes was evaluated using random effects meta-analyses. RR values were compared on the log scale, and the treatment effect was exponentiated to return to the RR scale. Mean differences were computed and compared separately for fish of different age classes (one, two or three winters at sea).

Random effects meta-analyses of the described outcomes were performed using the method of DerSimonian and Laird. The estimate of heterogeneity was taken from the inverse-variance of the random-effect model using the metan command in Stata (Borenstein et al., 2010, Dohoo et al., 2010, Sterne, 2009). The metan command in Stata generates an estimate of the Cochran's Q statistic, which tests for differences in effect sizes across studies, an estimate of the variance of effect sizes between studies (τ^2), and Higgins I^2 (hereafter denoted I^2), which is an estimate of the proportion of the observed variance that reflects true differences in effect size (Sterne, 2009, Borenstein et al., 2010):

$$I^2 = (Q - \frac{d.f.}{Q}) \times 100$$

where Q is Cochran's Q statistic, and d.f. is the degrees of freedom (number of studies minus 1). If I^2 is close to zero, then the observed variation between studies is assumed to be attributable to random variation, as opposed to variance in the true effect sizes. If I^2 is large, then the reasons for the observed variance should be evaluated (Borenstein et al., 2010, Dohoo et al., 2010, Rothman et al., 2008, Sterne, 2009).

Trial-level random effects meta-regression models using the metareg command in Stata were used to evaluate the association between selected variables and the log (RR). Restricted maximum likelihood (REML) methods were used to estimate the between-release group variance (τ^2).

Each variable's association with the log (RR) was first evaluated in an unconditional analysis. Some continuous variables were redefined as categorical variables if their relationship with the log (RR) was clearly non-linear (as determined by lowess curves and/or by adding polynomial terms to the regression models). Some groups of categorical variables were combined to avoid very small categories.

The variables were first assessed by univariate meta-regression, and variables with p-value <0.20 were considered candidates for multivariate meta-regression. In the multivariate analyses, only variables with a p-value < 0.05 were retained (Dohoo et al., 2010). The proportion of variance explained was estimated as

$$R^2 = 1 - \frac{\boldsymbol{\tau^2}\mathbf{unexplained}}{\boldsymbol{\tau^2}\mathbf{total}}$$

where $\tau^2_{unexplained}$ was estimated from the model including predictors, and τ^2_{total} was the unexplained between-trial variance from a null model.

Baseline risk, i.e., the proportion of recaptured fish in the control group (Dohoo et al., 2007), is defined in the following text as *baseline survival*. The rationale behind not using the more standard term, baseline risk, is that it is counterintuitive that an increased risk would lead to a higher survival estimate. Baseline survival was initially evaluated in the same manner as other potential causes of heterogeneity. However, because there is a structural relationship between baseline survival and the RR for the effect of treatment (the proportion of fish recaptured in the control group is the denominator of the RR for treatment effect), an alternative method of evaluating this specific effect was adopted (see below). By including baseline survival as a predictor variable, we assume that the variation in recapture in the control group reflects survival variation between release groups due to unmeasured risk factors affecting the release groups (Dohoo et al., 2007).

The meta-regression process was repeated to evaluate factors affecting the mean differences in weight at recapture.

Assessment of potential biases

Begg's and Egger's tests were used in combination with a funnel plot to assess potential publication bias (Borenstein et al., 2010, Dohoo et al., 2010, Sterne, 2009). An influence plot was used to identify any influential trials. Information biases were assessed using a quantitative bias assessment (QBA) with various levels of treatment efficacy (50-90%) assumed. Selection bias was evaluated by allowing recapture rates to differ by 10% between the treatment and control groups. The details of these methods are presented in the supplemental material.

As noted above, baseline survival is a component of the RR for treatment effect, and consequently, standard meta-regression techniques will produce biased estimates of the effect of baseline survival on the RR (Dohoo et al., 2007). A model was developed by Sharp and Thompson (2000) of the log odds of recapture, containing two correlated random effects terms to account for variation across studies. The random intercept accounts for variation in recapture rates across studies, and the random slope for treatment allows the effect of treatment to vary across studies. The correlation between these two random terms describes the manner in which baseline survival affects the RR for treatment. This model functions on the log odds scale as opposed to the log risk ratio scale used in the standard meta-regression, but because the recapture rates are so low, the two scales are comparable.

Two models were fit. The first replicated the final model determined from the standard meta-regression procedures to confirm that the estimates of effect of predictors other than baseline survival were not affected by the structural bias. Subsequently, a model with treatment as the sole predictor was fit to obtain an overall estimate of the effect of baseline survival on the estimate of treatment effect.

Analysis of factors affecting baseline survival

Because baseline survival appeared to be a very important predictor variable in the meta-regression analyses (see results), it was important to understand what variables affected baseline survival. All variables were first assessed by univariable linear regression, and variables with p-value <0.20 were considered candidates for multivariable linear regression (Table A1). In the multivariable analyses, only variables with a p-value < 0.05 were retained (Table 1).

Evaluation of impact of treatment (Attributable fraction)

The RRs reflect the relative effect of treatment on recapture risk. Attributable fractions (AF) reflect the proportion of additional recaptures that could be attributed to the effect of treatment and were computed as AF = (RR-1)/RR if RR>1 and 1-RR if RR<=1. A weighted average was computed using the same (inverse variance) weights as for the RR.

Results

Literature review and data processing

From the studies that contained relevant data, four published articles and two editorial comments/responses were excluded because they were from countries other than Norway (Gargan et al., 2012, Jackson et al., 2013, Jackson et al., 2011a, Jackson et al., 2011b, Krkošek et al., 2013, Krkošek et al., 2014).Two releases performed in Norway were excluded because they focused on sea trout (*Salmo trutta*, Salmonidae) rather than Atlantic salmon. Finally, a total of 118 smolt releases from 9 rivers and 1 fish farm location over 1996-2011 were identified by the systematic review and included in the study (Table 2 and Fig. 1). These releases were extracted from four published international peer-reviewed scientific papers (84 releases), four national reports (10 releases), and four non-published reports/assignments (26 releases). A listing of all extracted data is provided in the supplemental material.

A total of 17 releases had zero recaptured fish in both the treatment and control groups: eight from Vosso, seven from Dale and two from Halselv. These releases provided no information about treatment effect and were consequently excluded from all analyses. Of the remaining 101 releases, 14 contained release groups where either the control group or the treated group had zero recaptures. These releases were retained in the final dataset, but 0 was replaced with 0.5 to enable the computation of the log (RR). After exploring the weights of these release groups in the overall meta-analysis, they were all found to have very low weights, and they contributed very little to the final results.

Risk ratios across releases varied from 0.167 to 29.0. A histogram of the log (RR) is shown in figure 2.

Meta-analysis

The overall random effects meta-analysis of all the studies, including 101 release groups, estimated an overall RR of 1.18 (95 % confidence interval (CI): 1.07-1.30, $P<0.001$). However, there was a substantial amount of heterogeneity in the data, as revealed by an I^2 of 40.1% ($Q = 167.04$, P-value<0.001). The estimated between-study variance τ^2 was 0.0719.

The meta-analyses of the weight and length measurements of the recaptured fish indicated that treated fish returning after one winter at sea were significantly heavier than the controls (weighted mean difference = 123 grams, 95% CI: 45 - 200, P=0.002), but there were no significant treatment effects on weights in fish returning after two and three winters at sea fish or on length in any of the age groups. There was considerable variation between releases in terms of the mean difference in weights of fish returning after one winter at sea ($I^2 = 78\%$).

Meta-regression

The following variables were significant at a P-value <0.20 and were included in the multivariate analysis: release location, release period, temperature and baseline survival. In the final model, temperature along the migration route was not significant and was not retained. The variables release location, period and baseline survival were all significant (Table 3). Subsequent adjustment for the structural bias between baseline survival and RR (see Section 3.4) produced only minor changes in the coefficients for release location and period. Therefore, the results from the standard meta-regression were used for these factors for ease of understanding.

In the final model ($F_{5,97}=7.69$, $p<0.001$), I^2 was reduced to 13.9%, and the three retained variables explained 70.6% of the between-study variation. Baseline survival was a major predictor, and for a one unit increase in baseline survival, the log (RR) dropped by 0.24 units. However, baseline survival is a function of both actual variation in survival and recapture efforts. To evaluate the impact of recapture effort, we ran a new model including only data from Vosso and Dale, due to the relatively constant recapture effort over the years. This test did not alter the final model ($F_{5,63}=6.04$, $p<0.0001$), except that the I^2 value changed to 28.8 %, and the variance explained was 67.9 %. In short, the effect of baseline survival suggests that the RR is high when survival in the control group is low and low when survival in the control group is high.

The effect of one outlier with a very high risk ratio (release group in Dale River, 1997, Skilbrei et al. 2013) was tested by running the model excluding this data point. This test did not alter the final result ($F_{5,96}$ =6.73, p<0.0001, adjusted- R^2 =68.2, I^2=10.6 %).

The RR was highest during the first time period of releases (1996-2003) and then dropped to almost no effect of treatment during the second period (2004-2006), but increased again during the third period (2007-2008) and was almost back to the same level as in first period in the last period (2009-2011). The RR was higher in groups released in the fjord compared to groups released in the river or estuary.

The meta-regression of factors contributing to the heterogeneity (I^2= 78%) of the effects of treatment on the mean difference in weights of fish returning after one winter at sea was not very productive. The smolt migration distance was the only significant (P=0.03) factor, and it only explained 11% of the unexplained variation.

Bias

Publication bias was not expected, given that we included both published and non-published data in the meta-analyses. Neither tests for publication bias nor the funnel plot showed significant evidence of publication bias. When individual studies were examined, one release group in the Vosso river in a study by Barlaup (2013) did show considerable influence on the overall RR estimate (which would have been higher without this release group: 95 treated vs 142 controls recaptured -> RR = 0.69).

As the observed RR depended strongly on baseline survival, so did the apparent effect of changing treatment efficacy. Table 4 presents the results of the QBA of possible misclassification of treatment as a result of treatment efficacies less than 100%. In general, lower treatment efficacies were associated with underestimation of the RR for treatment if the baseline survival was low (particularly in the lowest quartile) but exhibited little effect if the baseline survival was high.

Selection bias arising from differential recapture rates in the treated and control group did not appear to have much effect on the RR. If the recapture rate in the treated group was 10% higher (or lower) than in the control group, the estimate of the RR also changed by approximately 10% (9-11%).

The full model accounting for the structural relationship between baseline survival and the RR (i.e., including release period and location) produced very similar estimates of effects for release location and period (details in supplementary material). However, the coefficient for baseline survival dropped from 0.248 to 0.147, suggesting that approximately 50% of the effect observed in the standard meta-regression was attributable to structural bias. A model with treatment as the sole predictor was used to obtain average treatment effects across years and locations. In this model, the coefficient for baseline survival was 0.105 (per unit log baseline survival). The estimated OR for treatment at low baseline survival (low control group recapture = 0.02%) was 1.7, and the estimated OR for treatment at high baseline survival (high control group recapture = 2 %) was 0.99 (Fig. 3).

Factors affecting baseline survival

The following variables were significant at a P-value <0.20 and were included in the multivariate analysis: release location (fjord versus river/estuary), river, temperature, release day, lice exposure (sum over 200 km), and distance migrated (distance from release to open ocean).

In the final model, lice exposure and release day were not significant and were consequently omitted. Lice exposure became insignificant in the final model due to its correlation with distance (rho=0.448), which was also the case for release location and distance migrated (rho=0.72). Distance was a better predictor of baseline survival than either lice exposure or release location, so these two variables were dropped from the model, leaving a final model that included river and migration distance ($F_{5,83}$ = 8.56, adjusted R^2=0.34, P<0.0001). This model predicted that baseline survival would decrease by 0.04 units (on a log scale) for every km migrated. Thus, groups of non-treated fish released 50 km from the river outlet (i.e., will have to migrate 50 km less to reach the ocean) will have a 7.1 times higher survival rate than non-treated fish released in the river or river outlet.

Attributable fraction

The distribution of AF values is shown in Figure 4, indicating a large variation in AF between studies. The weighted average value was 11.1% (CI: 4.4 – 17.9 %).

Discussion

Meta-analysis techniques were selected as the most appropriate method for both combining results from multiple studies and for evaluating why study results differed. In medicine and epidemiology, meta-analysis is generally considered to provide the highest level of evidence as to the effect of a treatment. "Potential advantages of meta-analyses include an increase in power (sic. to detect treatment effects), an improvement in precision, the ability to answer questions not posed by individual studies, and the opportunity to settle controversies arising from conflicting claims" (Higgins and Green, 2011).

Overall, the results from this meta-analysis suggest that treatment increases survival in the release groups (mean RR = 1.18, 95% CI: 1.07-1.3). This value is lower than what Krkošek et al. (2013) reported from a meta-analysis (1.39, 95% CI: 1.18 -1.42) based on mostly Irish and some Norwegian studies. Our data included more trials than did previous studies and also exhibited more heterogeneity because our analysis treated the releases as separate observations, while Krkošek et al. (2013) aggregated multiple releases in the same river and year into a single river-year observation. It is important to note that an average RR is an incomplete representation of the effect of treatment on the recapture of returning adult salmon. Consequently, although our main conclusion is that exposure to parasites is a significant contributor to the marine survival of Atlantic salmon, our secondary conclusion is that in some release groups, treatment was very beneficial, while in others, there was clearly no effect. This variation in treatment effect could be explained, in part, by where the fish were released, in what time period they were released and the baseline survival. The baseline survival was by far the most import source of heterogeneity. The most prevalent parasite in the region affected by the drugs administered was salmon louse. Hence, the meta-analysis supports the hypothesis that long-acting anti-parasitic treatment can protect salmon smolts from salmon lice during outward migration and that salmon lice is a contributor to the mortality of salmon.

Effect of baseline survival on estimate of treatment effect

After correcting for the structural dependency between baseline survival and the RR, the estimated RR at low baseline survival was 1.7, while at high baseline survival it was 0.99. This result suggests that if survival in the control group is generally good, then the risk ratio is low, while if survival is poor, the risk ratio is high. There are two main potential hypotheses regarding why we observe this strong relationship with baseline survival: (1) the detrimental effect of lice is exacerbated in situations when the salmon smolts also have to cope with increased pressure from other causes of mortality, and (2) there is large unmeasured variation in the exposure to lice between release groups that is driving variation in both baseline survival and the estimated treatment effect. In the second scenario, release groups with low survival will also be associated with high exposure to lice.

The first hypothesis could be explained by an interaction between salmon lice and other risk factors that the salmon encounter. For example, in years where prey conditions are poor, salmon lice can be detrimental for a starving smolt, while in years where prey conditions are good, the smolt will have fewer problems coping with the additional stress posed by the parasite. This explanation is consistent with the study by Connors et al. (2012), who found that the decline of pink salmon could be explained by a synergetic effect of climate, predation and salmon farm exposure. This explanation is also consistent with a recent experimental study by (Godwin et al., 2015), who demonstrated that sockeye salmon heavily infected with salmon lice are inferior competitors to lightly infected salmon. Furthermore, Finstad et al. (2007) showed experimentally that smolts with prior exposure to suboptimal water quality were more affected by salmon lice than smolts without such exposure.

The second hypothesis (2) suggests that baseline survival itself may, in part, be driven by salmon lice exposure. This explanation would mean that in release groups with high exposure to salmon lice, survival in the control group would be relatively, low and because lice exposure was higher, treatment effect would also be expected to be higher, and vice versa. If salmon lice exposure is mainly driven by the production of lice in fish farms, we would expect a correlation with baseline survival and lice exposure estimation from fish farms. There was a correlation between salmon lice exposure from fish farms and the log survival in the control group (rho=-0.25), but the salmon lice exposure could not explain the heterogeneity in the risk ratio (see below). Furthermore, lice exposure fell out of the final model when the distance the fish had to migrate to reach the ocean was included. However, it seems reasonable that there is a large variation in exposure between release groups due to spatial and temporal variation in salmon farm management practices (Bjorn et al., 2011) and to physical oceanographic variables important for lice dispersal (Asplin et al., 2014, Johnsen et al., 2014). Statistically, it is not possible to separate these hypotheses without much better data on lice exposure.

Absence of observed effect of sea lice exposures estimated from fish farms

None of the salmon lice exposure estimates from the production of lice from fish farms had any significant effects on the risk ratio estimates. This result could be explained by any of the following possibilities: (1) the additional salmon lice from fish farms do not affect the release groups, (2) the salmon lice exposure estimates do not represent the realized exposure of lice from fish farms, or (3) the efficacy of treatment is reduced for lice from fish farms due to resistance to treatment. The salmon lice exposure estimate based on a density kernel in combination with the assumed migration path of smolts used in this study ignores variation in ocean currents and the stratification of salmon lice according to salinity. Furthermore, the method integrates data on a time scale of months. Consequently, it is not surprising that the method does not precisely replicate the lice exposure for individual release groups. However, similar methods have recently been used to model the development of lice infections in naïve farmed fish from the onset of marine production (Kristoffersen et al., 2014). This study argues that farm production of lice is an important driver of lice transmission to naïve farmed salmon. However, extrapolating this method to the calculate exposure of migrating salmon smolts to farm-origin lice may not be valid. For example, the vertical distribution of smolts (Thorstad et al., 2012) and avoidance of low salinity waters by salmon lice (Heuch, 1995, Heuch et al., 1995) will strongly affect their interaction. Furthermore, while fish farms accumulate salmon lice over a longer time period, the exposure of salmon smolts to salmon lice most likely depends strongly on whether the smolts encounter dense patches of salmon lice (Penston et al., 2008, Penston and Davies, 2009). Using more detailed hydrodynamic models (Johnsen et al., 2014, Asplin et al., 2014) to estimate the spread and patchiness of infectious lice stages in waters of varying salinity could potentially give better explanatory power and should be explored. However, even though an appropriate model of distribution of salmon lice can be constructed, the question of where the salmon smolts migrate and how the release groups are distributed in the fjord system will also need to be determined. Studies on acoustically tagged fish clearly show that the migration patterns of Atlantic salmon smolts are highly variable and depend on both intrinsic and extrinsic factors that are known to vary within and between systems (Thorstad et al., 2012).

Change in effect of treatment over time

The effect of treatment also changed over the years. In the first period from 1996 to 2003, the risk ratio was relatively high, but it fell to almost no effect in the second period from 2004 to 2006. In the last two periods, the risk ratio rose again, and in the last period (2009-2012), it was similar to the first period. The data were divided into quartiles based on the number of release groups, after determining that the temporal trends were non-linear and that it was not possible to include the year as a categorical variable (too little data in many individual years). This impossibility precluded evaluating annual variability. Therefore, the study focused on the variation between larger time periods. The production of salmon lice from fish farms is mainly driven by the number of fish and the number of female lice per fish. During the last 10-15 years, there has been an increased focus on lowering the production of infective stages of salmon lice (copepodites) during the wild Atlantic smolt run in springtime in Norway. A coordinated spring delousing has been implemented and is currently mandatory across all regions in Norway. This development has manifested itself in a decreased abundance of female lice during springtime since 2002 (Jansen et al., 2012). Studies from other regions have suggested that spring delousing is an effective tool to protect wild migratory salmon smolts from salmon lice, given that effective treatment is used and sufficiently coordinated (Peacock et al., 2013). Meanwhile, however, the number of farmed fish (and consequently number of hosts) in most regions has increased steadily during the same period. A combination of these two patterns may explain the decreasing risk ratio from the first period to the second period and the subsequent increased risk ratio in the last two periods.

Bias

While studies from RCTs are often thought to give unequivocal answers regarding treatment effects, applying such methods to study the effects of parasites on wild fish is complex. While in traditional RCTs, the treatment efficacy is under scrutiny, the efficacy of treatment in studies with treated and untreated salmon smolts is assumed to be 100%, and any variation in treatment effect is treated as either natural variation or heterogeneity. However, there are several reasons why the results from release groups do not necessarily reflect the mortality patterns in wild fish.

Skilbrei et al. (2008) documented that when oral administration of emamectin benzoate is used, the resulting levels in tissue samples are very variable, with a proportion of the fish having levels below the recommended level within one week of administration. Similarly, Gargan et al. (2012) reported that 35 % of the sampled fish had tissue levels below the limit of detection (9 $\mu g \cdot kg^{-1}$). This resulted in a change from oral to inter-peritoneal injection (Glover et al., 2010) in the study by Skilbrei et al. (2013). It must therefore be expected that treated groups that were given treatment through oral administration were not 100% protected for the duration of their migration, and more than 50% of the release groups received oral administration.

Even when treatment is administered correctly, anti-parasitic agents may still not render 100% protection. Reduced sensitivity in some of the strains of lice collected at various fish farms along the coast were observed during the period of these experiments, i.e., in 2008 and 2009 (Horsberg, 2012, Espedal et al., 2013), and have developed further in recent years (Grøntvedt et al., 2015). Whether resistance has affected the results of our study is not known. However, it is assumed that resistance to emamectin benzoate in fish farms was not present at the beginning of the study period and might be more prevalent in the most recent years. This development may explain why some of the largest treatment effects were observed in the beginning of our data series.

Another assumption is that the effect of the treatment will last for 6-8 weeks and that this time period will be sufficient to protect smolts from lice (Stone 2000). This assumption requires that most exposure to salmon lice occurs during near-shore migration and that salmon smolts will migrate quickly from the near-shore habitat. However, while the estuary and fjord migration of Atlantic salmon smolts has been documented thoroughly by the use of different tagging equipment (e.g., acoustic transmitters; (Thorstad et al., 2012)), there is little documented information on how the fish migrate after leaving the fjord. One possibility is that the fish follow the coastal current northwards before migrating into the open ocean. In this case, exposure to salmon lice produced in fish farms can be decoupled from the fjord migration, and the treatment effect may not protect the fish during the entire period of exposure. There was a larger estimated effect size for groups released in the fjord compared to groups released in the river or estuary. If exposure to lice is mostly in the outer part of the fjords, and if treatment is most effective during the first period after release, the difference observed between the two groups could be because the release groups in the outer fjord encounter lice when they are effectively protected by the treatment, while release groups in the river encounter lice when they are less protected.

In theory, anti-parasitic agents may affect parasites other than salmon lice. Emamectin benzoate belongs to the group avermectins, which are broad-spectrum anti-parasitic agents (Jansson et al., 1997). If the smolts encounter other parasites during outward migration, the protection provided by emamectin benzoate may exert a beneficial effect on survival irrespective of salmon lice exposure. For example, sea trout in Scottish waters may have up to 100% prevalence of endoparasites such as parasitic nematodes (Anisakis sp., (Urquhart et al., 2010)), which may be affected by avermectins. However, to date, the only prevalent parasite documented in the region is salmon louse, and we therefore find it highly unlikely that the pattern is driven by another parasite. Furthermore, the other anti-parasitic treatment that was used was Substance EX, which is a chitin-inhibitor and is unlikely to affect parasites that do not change a chitin-shell during their life-cycle.

Extrapolating results from cultivated to wild fish

Studies using release groups of cultivated smolts usually attempt to mimic the migration time of wild fish from a river, but in most cases, the time of release is largely controlled by the growth and physiological state of the fish in the hatchery rather than determined by the optimal time to release them. In some studies, multiple releases are performed throughout the season to study the seasonal effect. Skilbrei and Wennevik (2006) demonstrated that the RR was much higher in groups released later in the season. However, salmon smolts are also known to desmoltify (Stefansson et al., 1998), and holding back fish may lead to suboptimal smolt quality, which may lead to an overestimation of the effect of salmon lice. Moreover, cultivated smolts may behave differently from wild fish. Jonsson et al. (1991) concluded that the survival and the ability to cope with different environmental challenges are much lower for cultivated fish than wild fish. Consequently, one source of the large variation in baseline survival may be attributed to variation in the quality of the cultivated smolts and the ability of these smolts to cope with environmental challenges. If the higher survival of wild smolts compared to cultivated smolts is due to the same factors that drive baseline survival, then the results of this study suggest that lice may have a smaller impact on wild smolts than we observe on cultivated smolts.

The results are also limited by the fact that most of the data (and hence, the weight of the analysis) come from a limited region just north of Bergen (Vosso, Dale & Matre Research Station). The results are also weighted heavily toward release groups that have been released in the outer region of the fjord because these groups have higher survival (and will therefore have higher weights in the meta-analysis). The high survival in these groups can be partially explained by the fact that these fish avoid predation during the transition through estuaries (Thorstad et al., 2012). Consequently, the weight of the dataset is on release groups with relatively low exposure compared to most large salmon populations in Norway entering the ocean through long fjord arms.

Conclusions

The results of this study are consistent with earlier studies that show significant but, on average, relatively small beneficial effect for the effect of anti-parasitic treatment on the marine survival of Atlantic salmon. However, the finding of a strong relationship between baseline survival and the effect of treatment against salmon lice is novel and underpins the point that average values from such studies are of little interest when attempting to extrapolate the results to potential effects on wild fish. The results of this study thus provide support for the hypothesis that salmon lice contribute to the mortality of salmon. However, the effect was not consistently present and was strongly modulated by other risk factors. Consequently, the results suggest that the population-level effects of salmon lice on wild salmon cannot be estimated independently of the other factors that affect marine survival.

Acknowledgements

The authors would like to thank Hege Folkestad at the library at UiB for help with establishing the search strategy in the systematic review. Thanks to Helge Skoglund and Shad Mahlum for commenting on an earlier version of the manuscript and production of map, and to Henrik Styhn for input related to the correction for systematic bias when using baseline survival. The meta-analysis was financed mainly by the Norwegian Seafood Research Fund (Project nr. 900932). In addition, Knut Wiik Vollset was financed through the Norwegian Research Council during the final editing of the manuscript (project nr. 243912/E50). The experiments were funded by the Norwegian Environment Agency, Uni Research Environment, Institute of Marine Research, Hordaland County Council, The Norwegian Institute for Nature Research, the European Commission DG Fisheries Contract. No. Q5RS-2002-00730 (SUMBAWS), fish farmers contributing to the organization "Vossolauget", and the power companies BKK and Statkraft.

References

Anderson, R.M., May, R.M. (1978) Regulation and Stability of Host-Parasite Population Interactions .1. Regulatory Processes. *Journal of Animal Ecology* **47,** 219-247. [In English].

Asplin, L., Johnsen, I.A., Sandvik, A.D., *et al.* (2014) Dispersion of salmon lice in the Hardangerfjord. *Marine Biology Research* **10,** 216-225. [In English].

Barlaup, B.T. (2013) Redningsaksjonen for Vossolaksen. DN-utredning, 222.

Bjoern, P.A., Finstad, B. (1998) The development of salmon lice (*Lepeophtheirus salmonis*) on artificially infected post smolts of sea trout (Salmo trutta). *Canadian Journal of Zoology/Revue Canadien de Zoologie* **76,** 970-977. [In English].

Bjorn, P.A., Sivertsgard, R., Finstad, B., Nilsen, R., Serra-Llinares, R.M., Kristoffersen, R. (2011) Area protection may reduce salmon louse infection risk to wild salmonids. *Aquaculture Environment Interactions* **1,** 233-244. [In English].

Borenstein, M., Hedges, L.V., Higgins, J.P.T., Rothstein, H.R. (2010) A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods* **1,** 97-111. [In English].

Connors, B.M., Braun, D.C., Peterman, R.M., *et al.* (2012) Migration links ocean-scale competition and local ocean conditions with exposure to farmed salmon to shape wild salmon dynamics. *Conservation Letters* **5,** 304-312. [In English].

Costello, M.J. (2006) Ecology of sea lice parasitic on farmed and wild fish. *Trends in Parasitology* **22,** 475-483. [In English].

Cushing, D.H. (1975) *Marine ecology and fisheries*, Vol., Cambridge University Press, Cambridge.

Dohoo, I., Martin, W., Stryhn, H. (2010) *Veterinary Epidemiologic Research,* Second edition edn Vol.

Dohoo, I., Stryhn, H., Sanchez, J. (2007) Evaluation of underlying risk as a source of heterogeneity in meta-analyses: A simulation study of Bayesian and frequentist implementations of three models. *Preventive Veterinary Medicine* **81,** 38-55. [In English].

Espedal, P.G., Glover, K.A., Horsberg, T.E., Nilsen, F. (2013) Emamectin benzoate resistance and fitness in laboratory reared salmon lice (*Lepeophtheirus salmonis*). *Aquaculture* **416,** 111-118. [In English].

Finstad, B., Bjoern, P., Grimnes, A., Hvidsten, N. (2000) Laboratory and field investigations of salmon lice [*Lepeophtheirus salmonis* (Kroyer)] infestation on Atlantic salmon (*Salmo salar* L.) post-smolts. *Aquaculture Research* **31,** 795-803. [In English].

Finstad, B., Kroglund, F., Strand, R., *et al.* (2007) Salmon lice or suboptimal water quality - Reasons for reduced postsmolt survival? *Aquaculture* **273,** 374-383. [In English].

Friedland, K.D., Shank, B.V., Todd, C.D., McGinnity, P., Nye, J.A. (2014) Differential response of continental stock complexes of Atlantic salmon (*Salmo salar*) to the Atlantic Multidecadal Oscillation. *Journal of Marine Systems* **133,** 77-87. [In English].

Gargan, P.G., Forde, G., Hazon, N., Russell, D.J.F., Todd, C.D. (2012) Evidence for sea lice-induced marine mortality of Atlantic salmon (*Salmo salar*) in western Ireland from experimental releases of ranched smolts treated with emamectin benzoate. *Canadian Journal of Fisheries and Aquatic Sciences* **69,** 343-353. [In English].

Glover, K.A., Samuelsen, O.B., Skilbrei, O.T., Boxaspen, K., Lunestad, B.T. (2010) Pharmacokinetics of emamectin benzoate administered to Atlantic salmon, *Salmo salar* L., by intra-peritoneal injection. *Journal of Fish Diseases* **33,** 183-186. [In English].

Godwin, S.C., Dill, L.M., Reynolds, J.D., Krkošek, M. (2015) Sea lice, sockeye salmon, and foraging competition: lousy fish are lousy competitors. *Canadian Journal of Fisheries and Aquatic Sciences* **72,** 8.

Grøntvedt, R.N., P.A., J., T.A., H., K., H., Tarpai, A. (2015) The surveillance programme for resistance to chemotherapeutants in L. salmonis in Norway. Surveillance programmes for terrestrial and aquatic animals in Norway.

Heuch, P.A. (1995) Experimental-Evidence for Aggregation of Salmon Louse Copepodids (Lepeophtheirus-Salmonis) in Step Salinity Gradients. *Journal of the Marine Biological Association of the United Kingdom* **75,** 927-939. [In English].

Heuch, P.A., Parsons, A., Boxaspen, K. (1995) Diel Vertical Migration - a Possible Host-Finding Mechanism in Salmon Louse (Lepeophtheirus-Salmonis) Copepodids. *Canadian Journal of Fisheries and Aquatic Sciences* **52,** 681-689. [In English].

Higgins, J.P.T., Green, S. (2011) *Cochrane Handbook for Systematic reviews of Interventions,* (The Cochrane Collaboration, Vol.

Hjort, J. (1914) Fluctuatons in the great fisheries of northern Europe viewed in the light of biological research. . *Rapports et Procès-verbaux des Réunions du Counseil international pour l´Exploration de la Mer* **20,** 228.

Horsberg, T.E. (2012) Avermectin Use in Aquaculture. *Current Pharmaceutical Biotechnology* **13,** 1095-1102. [In English].

Jackson, D., Cotter, D., Newell, J., *et al.* (2013) Impact of *Lepeophtheirus salmonis* infestations on migrating Atlantic salmon , *Salmo salar* L., smolts at eight locations in Ireland with an analysis of lice-induced marine mortality. *Journal of Fish Diseases* **36,** 273-281. [In English].

Jackson, D., Cotter, D., oMaoileidigh, N., *et al.* (2011a) Impact of early infestation with the salmon louse *Lepeophtheirus salmonis* on the subsequent survival of outwardly migrating Atlantic salmon smolts from a number of rivers on Ireland's south and west coasts. *Aquaculture* **319,** 37-40. [In English].

Jackson, D., Cotter, D., OMaoileidigh, N., *et al.* (2011b) An evaluation of the impact of early infestation with the salmon louse *Lepeophtheirus salmonis* on the subsequent survival of outwardly migrating Atlantic salmon, *Salmo salar* L., smolts. *Aquaculture* **320,** 159-163. [In English].

Jansen, P.A., Kristoffersen, A.B., Viljugrein, H., Jimenez, D., Aldrin, M., Stien, A. (2012) Sea lice as a density-dependent constraint to salmonid farming. *Proceedings of the Royal Society B-Biological Sciences* **279,** 2330-2338. [In English].

Jansson, R., Brown, R., Cartwright, B., Cox, D., Dunbar, D., Dybas, R. Emamectin benzoate: a novel avermectin derivative for control of lepidopterous pests. . (Proceedings of the 3rd International Workshop on Management of Diamondback moth and other crucifer pests MARDI, Kuala Lumpur, Malaysia, 1997). A. Sivapragasam, ed., City.

Johnsen, I.A., Fiksen, O., Sandvik, A.D., Asplin, L. (2014) Vertical salmon lice behaviour as a response to environmental conditions and its influence on regional dispersion in a fjord system. *Aquaculture Environment Interactions* **5**. [In English].

Jonsson, B., Jonsson, N., Hansen, L.P. (1991) Differences in Life-History and Migratory Behavior between Wild and Hatchery-Reared Atlantic Salmon in Nature. *Aquaculture* **98,** 69-78. [In English].

Kristoffersen, A.B., Jimenez, D., Viljugrein, H., Grontvedt, R., Stien, A., Jansen, P.A. (2014) Large scale modelling of salmon lice (*Lepeophtheirus salmonis*) infection pressure based on lice monitoring data from Norwegian salmonid farms. *Epidemics* **9,** 31-39. [In English].

Krkošek, M., Revie, C.W., Finstad, B., Todd, C.D. (2014) Comment on Jackson et al. 'Impact of *Lepeophtheirus salmonis* infestations on migrating Atlantic salmon, *Salmo salar* L., smolts at eight locations in Ireland with an analysis of lice-induced marine mortality'. *Journal of Fish Diseases* **37,** 415-417. [In English].

Krkošek, M., Revie, C.W., Gargan, P.G., Skilbrei, O.T., Finstad, B., Todd, C.D. (2013) Impact of parasites on salmon recruitment in the Northeast Atlantic Ocean. *Proceedings of the Royal Society B-Biological Sciences* **280**. [In English].

May, R.M., Anderson, R.M. (1978) Regulation and Stability of Host-Parasite Population Interactions .2. Destabilizing Processes. *Journal of Animal Ecology* **47,** 249-267. [In English].

Peacock, S.J., Krkošek, M., Proboszcz, S., Orr, C., Lewis, M.A. (2013) Cessation of a salmon decline with control of parasites. *Ecological Applications* **23,** 606-620. [In English].

Penston, M.J., Davies, I.M. (2009) An assessment of salmon farms and wild salmonids as sources of *Lepeophtheirus salmonis* (Kroyer) copepodids in the water column in Loch Torridon, Scotland. *Journal of Fish Diseases* **32,** 75-88. [In English].

Penston, M.J., Millar, C.P., Zuur, A., Davies, I.M. (2008) Spatial and temporal distribution of *Lepeophtheirus salmonis* (Kroyer) larvae in a sea loch containing Atlantic salmon, *Salmo salar* L., farms on the north-west coast of Scotland. *Journal of Fish Diseases* **31,** 361-371. [In English].

Rothman, K.J., Greenland, S., Lash, T.L. (2008) *Modern epidemiology,* Vol., Lippincott Williams & Wilkins.

Sharp, S.J., Thompson, S.G. (2000) Analysing the relationship between treatment effect and underlying risk in meta-analysis: comparison and development of approaches. *Statistics in Medicine* **19,** 3251-3274. [In English].

Skilbrei, O.T., Espedal, P.G., Nilsen, F., Garcia, E.P., Glover, K.A. (2015) Evaluation of the use of emamectin benzoate and substance EX as preventive treatments against salmon lice infestation in sea-ranched Atlantic salmon smolts. . *Diseases of Aquatic Organisms* **113,** 187-194.

Skilbrei, O.T., Finstad, B., Urdal, K., Bakke, G., Kroglund, F., Strand, R. (2013) Impact of early salmon louse, *Lepeophtheirus salmonis*, infestation and differences in survival and marine growth of sea-ranched Atlantic salmon, *Salmo salar* L., smolts 1997-2009. *Journal of Fish Diseases* **36,** 249-260. [In English].

Skilbrei, O.T., Glover, K.A., Samuelsen, O.B., Lunestad, B.T. (2008) A laboratory study to evaluate the use of emamectin benzoate in the control of sea lice in sea-ranched Atlantic salmon (*Salmo salar* L.). *Aquaculture* **285,** 2-7. [In English].

Skilbrei, O.T., Wennevik, V. (2006) Survival and growth of sea-ranched Atlantic salmon, *Salmo salar* L., treated against sea lice before release. *Ices Journal of Marine Science* **63,** 1317-1325. [In English].

Stefansson, S.O., Berge, A.I., Gunnarsson, G.S. (1998) Changes in seawater tolerance and gill Na+,K+-ATPase activity during desmoltification in Atlantic salmon kept in freshwater at different temperatures. *Aquaculture* **168,** 271-277. [In English].

Sterne, J.A.C. (2009) *Meta-Analysis in Stata: An Updated Collection from the Stata Journal,* Vol., Stata Press.

Thorstad, E.B., Whoriskey, F., Uglem, I., Moore, A., Rikardsen, A.H., Finstad, B. (2012) A critical life stage of the Atlantic salmon *Salmo salar*: behaviour and survival during the smolt and initial post-smolt migration. *Journal of Fish Biology* **81,** 500-542. [In English].

Torrissen, O., Jones, S., Asche, F., *et al.* (2013) Salmon lice - impact on wild salmonids and salmon aquaculture. *Journal of Fish Diseases* **36,** 171-194. [In English].

Urquhart, K., Pert, C.C., Fryer, R.J., *et al.* (2010) A survey of pathogens and metazoan parasites on wild sea trout (*Salmo trutta*) in Scottish waters. *Ices Journal of Marine Science* **67,** 444-453. [In English].

Vollset, K.W., Barlaup, B.T., Skoglund, H., Normann, E.S., Skilbrei, O.T. (2014) Salmon lice increase the age of returning Atlantic salmon. *Biol Lett* **10,** 20130896.
Wagner, G.N., Fast, M.D., Johnson, S.C. (2008) Physiology and immunology of *Lepeophtheirus salmonis* infections of salmonids. *Trends in Parasitology* **24,** 176-183. [In English].
Wells, A., Grierson, C.E., MacKenzie, M., *et al.* (2006) Physiological effects of simultaneous, abrupt seawater entry and sea lice (*Lepeophtheirus salmonis*) infestation of wild, sea-run brown trout (*Salmo trutta*) smolts. *Canadian Journal of Fisheries and Aquatic Sciences* **63,** 2809-2821. [In English].

Table 1. Variables used in meta-regression in a systematic review and meta-analysis of Norwegian trials/releases estimating the effects of anti-parasitic treatment of smolts on the marine survival of Atlantic salmon.

Predictor variable	Grouping/response	Type	Pooling
Publication type	Peer-review, other	Categorical	
Release location	Fjord, river/estuary	Categorical	River and estuary releases pooled
Release river	Southern rivers (Imsa, Årdal, Suldalslågen), Vosso, Dale, Matre and Northern rivers (Eira, Surna, Orkla, Halselv)	Categorical	Rivers pooled into 5 groups
Period	1996-2003, 2004-2006, 2007-2008, 2009-2012	Categorical	Release years pooled into four periods (release quartiles)
Release day	Days after May 1st	Continuous	
Treatment type	Emamectin in feed, Emamectin injected, Substance EX	Categorical	
Lice exposure	Density kernel 50 meter (sum)	Continuous	
Lice exposure	Density kernel 50 meter (max)	Continuous	
Lice exposure	Density kernel 200 meter (sum)	Continuous	
Lice exposure	Density kernel 200 meter (max)	Continuous	
Distance	Distance migrated from release to 200 km boarder (m)	Continuous	
Temperature	Average temperature in migration path (C°)	Continuous	
Release weight	Average weight of smolt group at release (g)	Continuous	
Baseline survival	Natural log of percent recaptured in control group	Continuous	

Table 2. Summary of the 118 Norwegian trials/releases used in in the systematic review and meta-analysis of Norwegian trials/releases estimating the effects of anti-parasitic treatment of smolts on the marine survival of Atlantic salmon. (C= Control, T = Treated). * indicates that unpublished data on multiple SW salmon are also included in the analysis that were not reported in publication. n.a. indicates “not available”.

				Smolts released (N)		Adults recaptured (N)	
River	Author	Publication year	Release groups (N)	C	T	C	T
Halselv	Hazon et al. 2006*	2007	3	6156	5958	21	17
Halselv	Strand og Finstad	2010	1	3365	4426	0	0
Orkla	Hvidsten et al. 2007	2007	2	5913	5901	32	62
Surna	Hvidsten et al. 2007	2007	1	2985	3000	51	66
Eira	Jensen et al. 2013	2013	4	12112	11796	33	34
Matre	Skilbrei et al. (Unpublished)	n.a.	18	31965	32045	98	111
Vosso	Barlaup et al. 2013	2013	37	158366	160826	947	1058
Dale	Skilbrei et al. 2012	2012	44	73068	77200	498	615
Dale	Skilbrei et al. (Unpublished)	n.a.	3	8165	8115	92	125
Suldalslågen	Finstad et al. (Unpublished)	n.a.	3	15995	15497	1	3
Imsa	Hazon et al. 2006*	2006	2	6000	4000	65	44
Årdal	Lehmann et al. (Unpublished)	n.a.	2	6385	6385	13	9

Table 3. Results from the multivariate random effects meta-regression on Norwegian trials estimating the effects of anti-parasitic treatment of smolts on the marine survival of Atlantic salmon. Variables and levels are separated by increased indentation. The standard error (SE) of the risk ratio is indicated in parenthesis. The baseline of the log risk ratio is equal to the intercept. Baseline survival is a variable in the model equal to the proportion of recaptured fish in the control group. Note that this model has not considered the structural dependence between the RR and baseline survival (Dohoo et al., 2007).

Variable and level	**Log risk ratio (SE)**	**P**	**95% confidence interval**	
Release location				
River/estuary	Baseline	-	-	
Fjord	0.185 (0.09)	0.036	.013	.357
Release year period[b]				
1996-2003	Baseline	-	-	
2004-2006	-0.512 (0.16)	0.002	-.833	-.191
2007-2008	-0.231 (0.14)	0.094	-.502	.040
2009-2012	-0.116 (0.10)	0.249	-.315	.083
Baseline survival [a]	-0.241 (0.05)	<0.00	-.337	-.144
Intercept	0.500(0.10))	<0.00	0.302	0.698

[a] centered at mean value of -5.793; the overall P-value for release year was P=0.0174.

Table 4 Estimated % change in risk ratio estimates for different assumed treatment efficacies divided into different quartiles of baseline survival (proportion of control group recaptured). "Consensus" was a trapezoidal distribution (50-75-90-98%) based on a consensus opinion about the distribution of efficacy across trials.

Treatment efficacy	Quartiles			
	Q1	**Q2**	**Q3**	**Q4**
100 %	0.0	0.0	0.0	0.0
90 %	9.7	6.3	0.0	-1.1
75 %	25.8	18.8	7.7	-2.1
50 %	67.7	43.8	23.1	-5.1
Consensus	16.1	12.5	7.7	-2.1

Figure legends

Figure 1 - Locations of smolt releases along the coastline of Norway. Locations of fish farms (kart.fiskdir.no, accessed 01.10.2014) are indicated with grey dots. The release locations are given symbols according to the pooling in the meta-analysis (circles=Imsa, Suldalslågen & Årdal, squares=Vosso, crosses=Dale, diamonds=Matre, triangles=Eira, Surna, Orkla, Halselv)

Figure 2 Distribution of log (risk ratios) of treatment trials estimating the effects of anti-parasitic treatment of smolts on the marine survival of Atlantic salmon in Norway from 1996-2011. Values >0 indicate a protective effect of treatment (i.e., enhanced recapture), while values <1 indicate a detrimental effect.

Figure 3 Scatter plot of estimates of OR of treatment derived from a model that accounts for the structural association between baseline survival and OR. Points are based on an estimate of OR that includes the random effect for the trial. Line shows relationship between baseline survival and OR. Two outlying data points (OR=2.80, baseline survival=4.71, and OR=2.99, baseline survival=2.53) were omitted from the graph to improve the scale. (Omission had no effect on the line shown.)

Figure 4 Distribution of estimated attributable fractions from all smolt releases in Norway from 1996-2011. Values >0 indicate a protective effect of treatment (i.e., enhanced recapture), while values <1 indicate a detrimental effect.

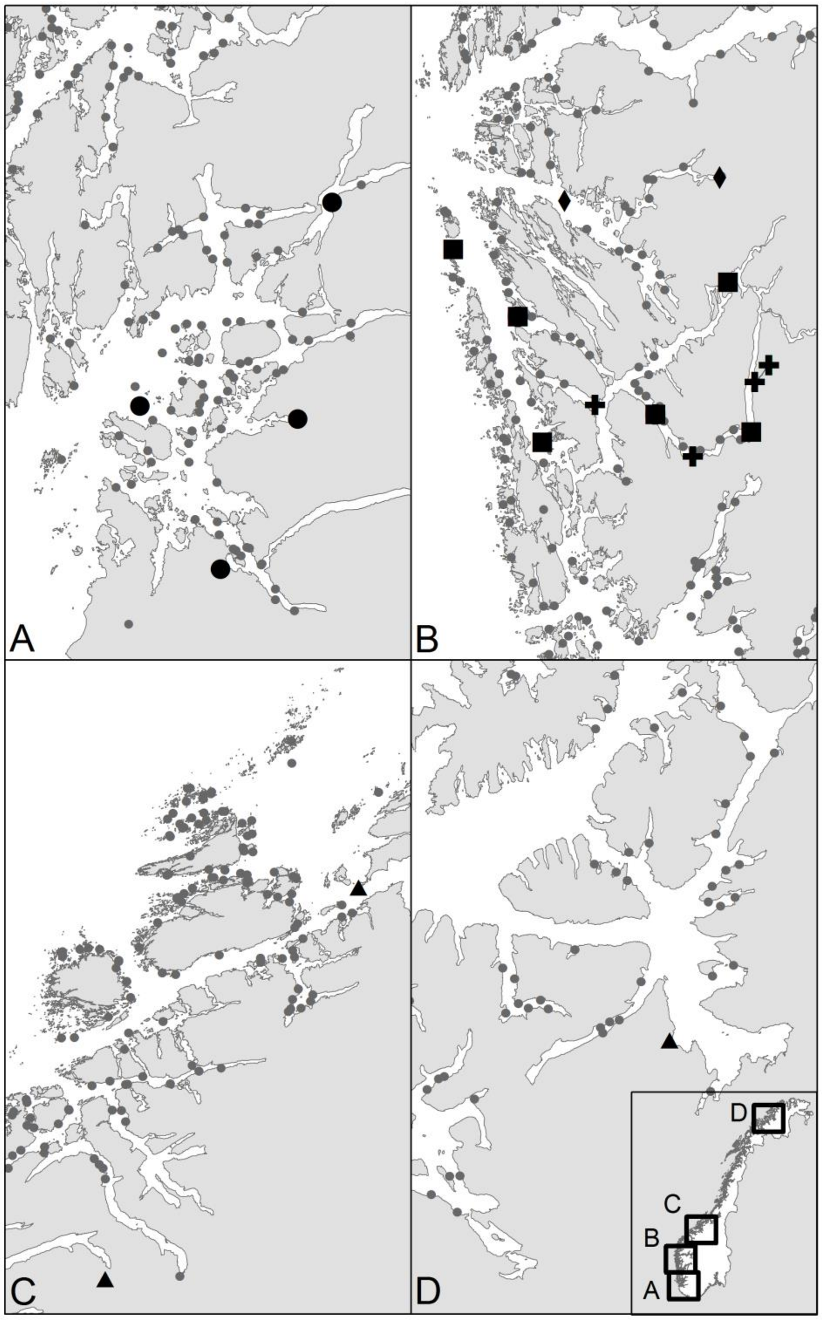

Figure 1

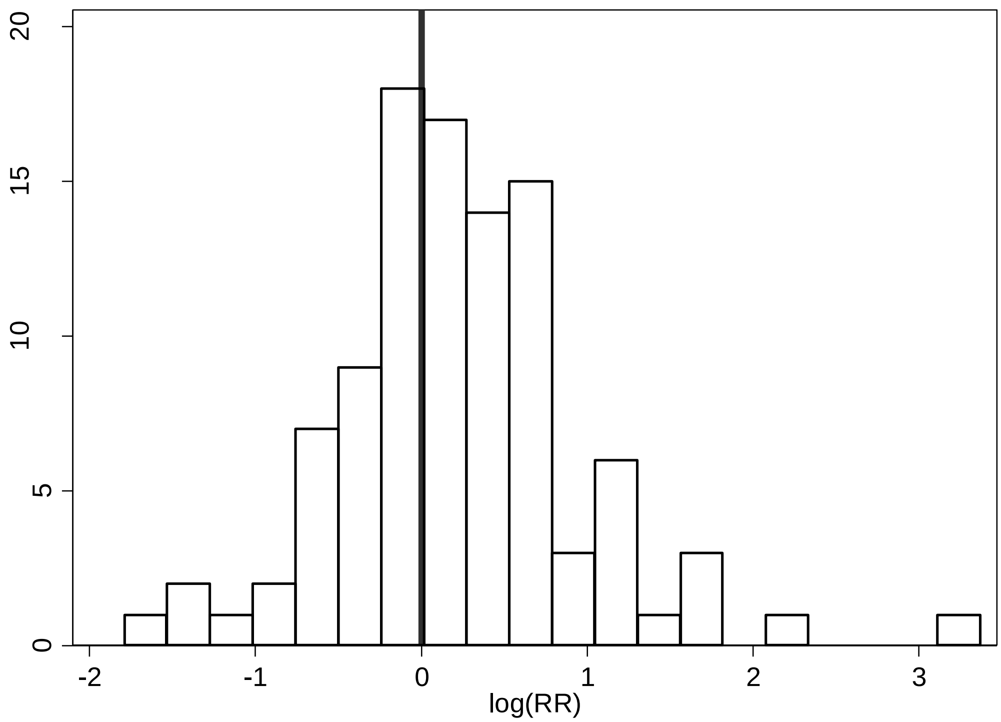

Figure 2

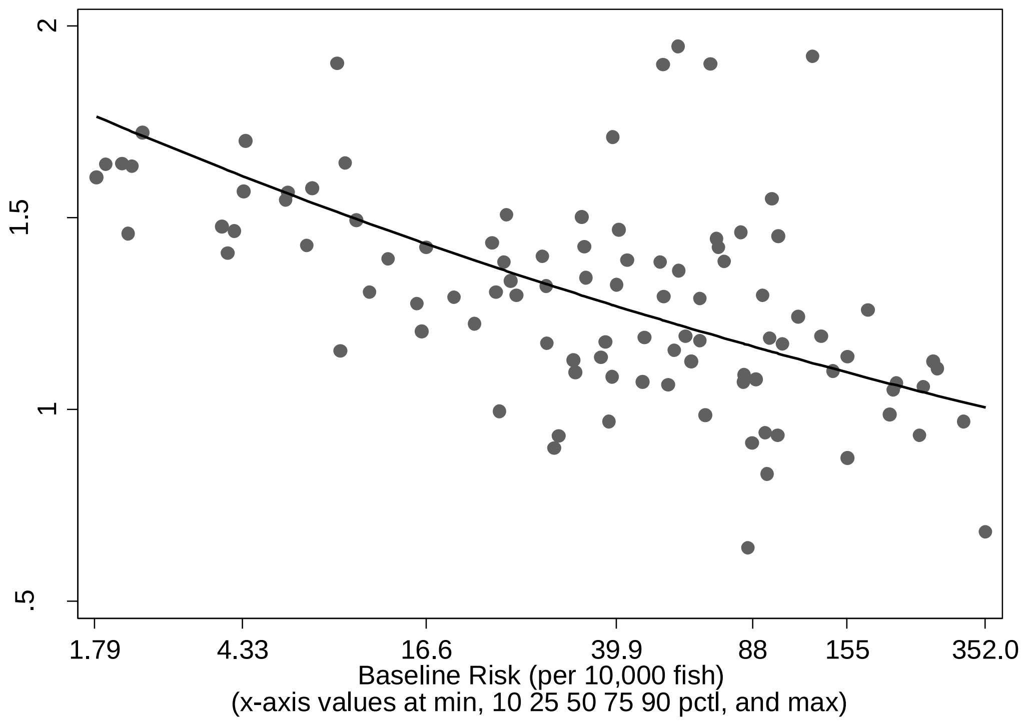
2
1.5
1
.5
1.79
4.33
16.6
39.9
88
155
352.0
Baseline Risk (per 10,000 fish)
(x-axis values at min, 10 25 50 75 90 pctl, and max)

Figure 3

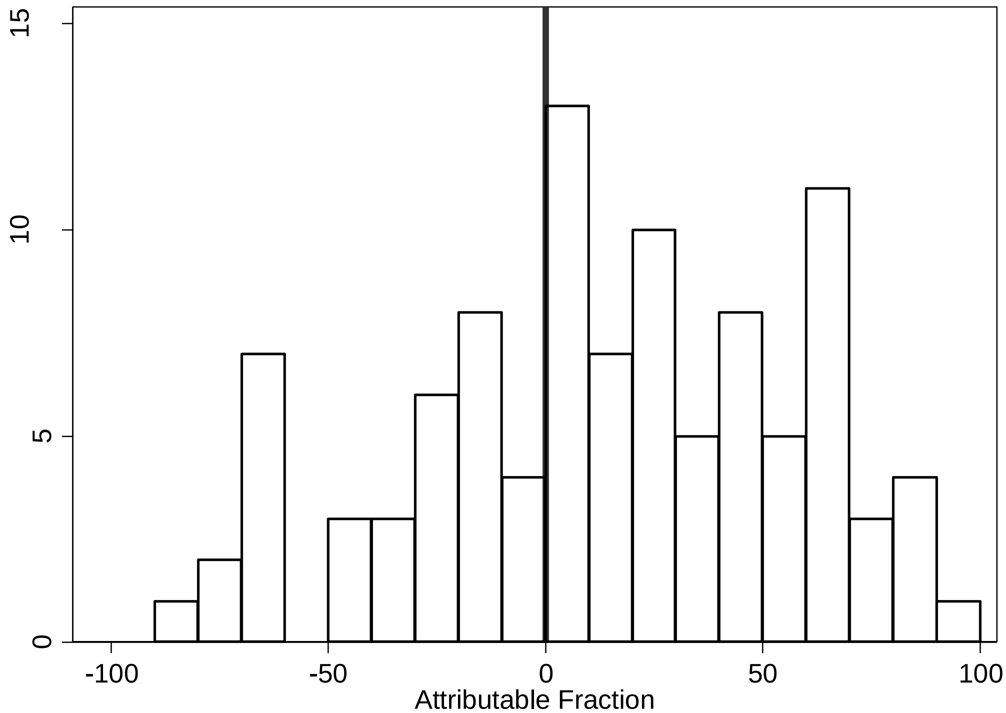

Figure 4