Pneumonia after bacterial or viral infection preceded or followed by radiation exposure - a reanalysis of older radiobiological data for discussion on low dose radiotherapy for COVID-19 pneumonia

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Abstract

Currently, there are at least 14 ongoing clinical studies on low dose radiotherapy (LDRT) for COVID-19 pneumonia in seven countries. One of the underlying assumptions is that irradiation at the level of 0.5–1.5 Gy is effective at ameliorating viral pneumonia. Its rationale, however, relies on early human case studies or animal studies mostly obtained in the pre-biotic era, where rigorous statistical analyses were not performed. It therefore remains unclear whether those early data would support such assumptions. With state-of-the-art statistical models, we re-analyzed eleven radiobiological animal datasets (generally dating from the 1920s to early 1970s) in which animals received moderate doses of radiation before or after bacterial or viral inoculation. A number of different model systems (guinea pigs, dogs, cats, mice) and types of challenging infection, both bacterial and viral, are considered. For post-inoculation radiation exposure (which is more relevant to LDRT for COVID-19 pneumonia) the results are heterogeneous, with one study (of six) showing a significant increase in risk associated with radiation exposure, another showing a significant decrease in risk associated with radiation exposure, and all other results being non-significant. For pre-inoculation exposure the results are also heterogeneous, with four (of six) datasets showing significant increase in risk associated with radiation exposure and the other two showing a significant decrease in risk. Collectively, these data do not suggest that there are strong modifying effects of radiation exposure after inoculation. Although there are stronger indications of modifications of risk by radiation exposure before inoculation, the inconsistency of direction of effect makes this body of data difficult to interpret.
Introduction

Low dose radiotherapy (LDRT) for Coronavirus Disease 2019 (COVID-19) pneumonia was proposed in early April 2020 (1,2). At least 14 clinical studies are currently ongoing in 7 countries (3). The rationale for clinical benefit (i.e., effectiveness of irradiation at the level of 0.5–1.5 Gy in treating viral pneumonia) largely relies on early human case studies or animal studies mostly obtained in the pre-biotic era, when a number of attempts were made to treat various non-cancer diseases with ionizing radiation, including virally- or bacterially-associated pneumonia. An influential paper underlying a number of proposals made for use of LDRT to treat COVID-19 pneumonia (1,2) was Calabrese and Dhawan in 2013 (4) who reviewed 19 papers, mostly case reports, describing outcomes from low dose radiotherapy with X-rays (LDRT) for pneumonia, among them 3 papers published in 1905–1916 and 16 published between 1925–1943. Their review identified a total of 863 cases, among which 717 showed good clinical response within three days of treatment (4). However, the human data reviewed were limited to case series, many based on small numbers of subjects. As the sampling framework in these case reports is unknown, they are subject to ascertainment bias and are effectively uninterpretable. The doses used are also often unknown. Calabrese and Dhawan (4) also identified four radiobiological studies, all from experiments done in the 1940s, namely Fried (5) using a guinea pig model, Lieberman et al. (6) using a canine model, Baylin et al (7) using a cat model, and Dubin et al. (8) using a murine model, the first two of these for bacterially-induced pneumonia and the last two for virally-induced pneumonia. For reasons that are not clear there are at least eight relevant radiobiological studies that were not considered in the review of Calabrese and Dhawan (4). Calabrese and Dhawan (4) did not attempt any statistical reanalysis of this old data. The aim of the present paper is to look at more nearly the totality of radiobiological data relating to radiation exposure before or after
inoculation with a viral or bacterial agent likely to result in pneumonia. Because of the age of the data being considered there are shortcomings in the original statistical analysis that was performed – indeed in all but a few cases (9,10) there does not appear to have been any formal statistical analysis in the original reports. It is the purpose of this paper to report reanalysis of this data so far as that is achievable, using state-of-the-art statistical survival models in order to assess modification of pneumonia morbidity or mortality risk by radiation exposure before or after inoculation.

**Methods**

We aimed to capture all radiobiological datasets relating to moderate or low dose radiation therapy whether given before or after viral or bacterial inoculation leading to pneumonia. We searched literature by means of a PubMed search (using terms ((radiation OR radiotherapy) AND pneumonia AND viral AND animal) OR ((radiation OR radiotherapy) AND pneumonia AND bacterial AND animal)) conducted on 2020-8-8, which returned 184 articles. We also searched for citations of the articles of Fried (5), Lieberman *et al.* (6), Baylin *et al.* (7), and Dubin *et al.* (8) on the same date. We did not restrict by date or language of the publication. We selected from these searches all relevant articles with information on LDRT and bacterially- or virally-induced pneumonia. The datasets used are listed in Table 1. It should be noted that the datasets we used include three of the four cited by Calabrese and Dhawan (4), but did not include the paper of Fried (5) which we judged did not contain any quantitatively useful information. We convert the given free-in-air dose in rad or rep in all studies to Gy via the scaling 1 rad/rep =0.00877 Gy (11).

*Statistical methods*
Mortality and morbidity risks in the radiobiological cohorts of Murphy and Sturm (12), Lieberman et al. (6) and Dubin et al. (8) were assessed using a Cox proportional hazards models (13), with time after radiation exposure, if that followed the inoculation, or time after bacterial or viral inoculation, if that followed the radiation exposure, as timescale, in which the relative risk (RR) (=hazard ratio) of death for animal \( i \) at time \( a \) after inoculation was given by a linear model in dose:

\[
RR_i[a, D_i | \alpha] = [1 + \alpha D_i]
\]  
(1)

or alternatively using a log-linear model in dose:

\[
RR_i[a, D_i | \alpha] = \exp[\alpha D_i]
\]  
(2)

where \( D_i \) is the total dose (in Gy), \( \alpha \) is the excess relative risk coefficient (ERR) per unit dose (Gy). For the dataset of Murphy and Sturm (12) the only usable information available is the fact of irradiation of the mice (yes or no), so that the model fitted is of the form:

\[
RR_i[a, 1_{\text{exposure}} | \alpha] = \exp[\alpha 1_{\text{exposure,=yes}}]
\]  
(3)

For most of the other datasets a linear logistic model is fitted to the data (generally on number of animals died in each group):

\[
P_i[a, D_i | \alpha_0, \alpha_1] = \exp[\alpha_0][1 + \alpha_1 D_i]/[1 + \exp[\alpha_0][1 + \alpha_1 D_i]]
\]  
(4)

Occasionally the more standard log-logistic model is fitted to the data (generally on number of animals died in each group):

\[
P_i[a, D_i | \alpha_0, \alpha_1] = \exp[\alpha_0 + \alpha_1 D_i]/[1 + \exp[\alpha_0 + \alpha_1 D_i]]
\]  
(5)

For the data of Fried (14), numbering only 7 animals and using as outcome improvement in pneumonia in relation to unirradiated controls, an exact logistic model was used (15), as non-exact methods did not converge. It is well known that the excess odds ratio approximates to the excess...
relative risk (16). All confidence intervals (CIs) and two-sided $p$-values are profile-partial-likelihood based (17). In the murine dataset of Dubin et al. (8) in various subgroups risks were assessed in relation to radiation dose administered after inoculation or dose before inoculation. In the murine dataset of Quilligan et al (18) pre-inoculation dose was given to all animals. There is some uncertainty associated with the number of mice in the first of the control groups in this dataset, so a range is employed, spanning the plausible range of 6-10 mice. The model was stratified by the three experiments reported in the data of Dubin et al. (8) and by the three groups used by Lieberman et al. (6). Tables 3 and 8 and Figure 1 and 2 show the risks in relation to dose for these two datasets. In the analysis of the data from Hale and Stoner (19) in some cases adjustment was made for the type of challenging infection. In the fits to the pneumonia intensity data of Baylin et al. (7) we used either log-logistic regression (as described above) comparing each pneumonia intensity group and those with greater intensity vs every group with reduced intensity; we also used ordinal regression with log-linear link (20) fitting to all the ordered intensity groups. In fits of the days of infection data of Baylin et al. (7) we used a linear regression model, estimating the CIs via the bias-corrected advanced method (21). All models were fitted via Epicure (22), R (23) or LogXact (15).

**Results**

*Irradiation after inoculation*

Table 2 demonstrates that there are weak indications ($0.05 < p < 0.1$) of decreased risk of pneumonia with post-inoculation dose in the dataset of Fried (14), whether for all guinea pigs or restricting to the six guinea pigs receiving *Staphylococcus aureus* inoculation. Table 3 demonstrates that there is a highly significant decreasing trend ($p<0.001$) of mortality with post-
inoculation dose in the dataset of Lieberman et al. (6) with EOR per Gy = -0.23 (95% CI -0.24, -0.16), as also shown by Figure 1. However, Table 3 shows that this is largely driven by a single group, group 3, as also shown by Figure 2. There is a non-significant positive trend with dose ($p>0.4$) in the murine data of Tanner and McConchie (24) (Table 4 and Figure 4).

There are few indications of trend of degree of pneumonia infection with dose in the feline data of Baylin et al. (7), whether using logistic or ordinal models (Table 5). However, Table 6 indicates that there is a significant decreasing trend of days of acute infection with dose in this dataset, with days of infection / Gy changing by -2.56 (95% CI -4.59, -0.33) ($p=0.015$), i.e., duration of infection decreasing with dose, as also shown by Figure 3. Table 7 demonstrates that there is a highly significant ($p<0.001$) increased risk of death associated with X-ray exposure after inoculation with *Pneumococcus* in the murine data of Murphy and Sturm (12), with RR = 3.67 (95% CI 1.84, 7.61).

**Radiation administration before and after inoculation**

Table 8 demonstrates that there is no significant trend ($p>0.4$) with post-inoculation dose in the data of Dubin et al. (8), whether using linear or log-linear models, which is confirmed also by Figure 1. However, there is a borderline significant decreasing trend ($p=0.03$) of mortality with pre-inoculation dose in this dataset, with EOR/Gy = -0.62 (95% CI -0.90, -0.09) again confirmed by Figure 1.

**Irradiation before inoculation**

Table 9 indicates that there is a highly significant ($p<0.001$) increase in risk in the C57BL mouse data of Quilligan et al (18) associated with post-influenza-inoculation radiation dose with EOR/Gy ranging from 3.73 (95% CI 0.42, 85.85) to 4.75 (95% CI 0.56, 108.10) depending on how many mice are assumed to be in the first control group. Table 10 shows that there is generally highly
significant ($p<0.005$) increase in risk associated with radiation before inoculation with influenza virus, *pneumococcus* type III bacterial infection or *Trichinella spiralis* larval infection in Swiss mice data of Hale and Stoner (19), whether adjusted or not for type of first immunizing infection, so that for example with such adjustment and excluding the *Trichinella spiralis* challenge infections the EOR/Gy = 1.71 (95% CI 0.97, 3.02). Pneumonitis morbidity and mortality were significantly decreased ($p<0.001$) after 3.5 Gy whole body air dose exposure in adult male albino CF-1 mice in the data of Berlin (9), so that for pneumonitis morbidity the EOR/Gy = -0.24 (95% CI -0.28, -0.17) and for pneumonitis mortality the EOR/Gy = -0.21 (95% CI -0.26, -0.14), as shown in Table 11. In contrast Table 12 and Figure 5 show reanalysis of slightly later data of Berlin and Cochran (10), which exhibits slightly heterogeneous results, with one set of experiments (given in Table III of Berlin and Cochran (10)) indicating a significant increase ($p<0.05$) in influenza mortality, whether or not adjusted for mode of administration of virus, but a different experimental set (reported in Table II of the paper) showing no significant effect ($p>0.1$) of radiation exposure on influenza morbidity or mortality. These experiments use a similar murine system, also given 3.5 Gy whole body air-dose exposure, as in the earlier paper of Berlin (9). Lundgren *et al* (25) used a novel type of radiation exposure, aerosolized $^{144}$CeO$_2$, which delivers localized $\beta$ dose to the lungs of C57BL/6J mice. As can be seen from Table 13 there was a small but highly significant increase in mortality risk associated with radiation exposure, with EOR/Gy = 0.008 (95% CI 0.002, 0.019, $p=0.002$).

**Discussion**

We have re-analyzed eleven radiobiological animal datasets, dating from the 1920s to the early 1970s, in which bacterial or viral agents were administered to induce pneumonia in animals that
were also exposed to moderate doses of radiation before or after inoculation. The statistical analysis in the original papers was limited, indeed in all but two cases (9,10) there does not appear to have been any formal statistical analysis. We therefore judged it necessary to statistically reanalyze the original datasets with something like state-of-the-art statistical models.

For post-inoculation radiation exposure the results are heterogeneous, with one study (of six), that of Murphy and Sturm (12), showing a significant increase in mortality risk associated with radiation exposure, another, that of Lieberman et al (6) showing a significant decrease in risk associated with radiation exposure (albeit driven by a single experimental group), and all other results being non-significant. For pre-inoculation exposure the results are also heterogeneous, with four (of six) datasets showing significant increase in risk associated with radiation exposure (at least for certain endpoints), namely those of Hale and Stoner (19), Berlin and Cochran (10), Quilligan et al (18) and Lundgren et al (25) and the other two, those of Dubin et al (8), and Berlin (9) showing a significant decrease in risk after radiation exposure. The reasons for this heterogeneity may be connected with the different model systems (dogs, cats, mice) being used, also possibly because of the various types of challenging infection, which included both bacterial agents (*Pneumococcus* types I, III, *Staphylococcus aureus haemolyticus*) and viral ones (swine influenza, feline, Thylers mouse encephalitis, influenza type A, CAM A-prime influenza, influenza A/PR8, and influenza A₀) (see Table 1).

Altogether, early radiobiology data do not suggest that there are strong modifying effects of radiation exposure after inoculation. In particular, the heterogeneity in the results of our statistical analysis suggest that these early datasets do not serve as supportive evidence that LDRT of infected individuals reduces mortality. Although there are stronger indications of modifications of risk by radiation exposure before inoculation, the inconsistency of direction of effect makes this body of
data difficult to interpret and has little relevance to LDRT for COVID-19 pneumonia – it would be unethical to conduct irradiation prior to infection.

Rödel et al (26) reviewed some of the epidemiological and radiobiological literature on LDRT. While acknowledging limitations in understanding the possible mechanism, Rödel et al (26) suggested that LDRT may stimulate anti-viral immunity via the modulating effects of type I interferons in the early stages of SARS-CoV-2 infection. Rödel et al (26) concluded that LDRT with a single dose of 0.5 Gy to the lungs warranted clinical investigation, while acknowledging the need for strict monitoring and disease phase-adapted treatment based on lung function tests and clinical markers (e.g. IL-6 and D-dimer in serum). Schaue and McBride (27) echoed some of the concerns of Rödel et al (26) on the importance of correctly timing the use of LDRT in treatment of SARS-CoV-2, but were much more cautious, and suggested that, for example, it was unlikely that LDRT would effectively counter the virally-induced cytokine storm that is a feature of the more severe forms of infection. Schaue and McBride (27) and even more forcefully Kirsch et al (28) suggested that the known deleterious adverse late health effects of 0.5-1.5 Gy administered to the lungs via increased risk of cancer and circulatory disease must be weighed against the unknown therapeutic benefits of LDRT. Kirsch et al concluded that “based on the available data, the potential risks of such [LDRT] trials outweigh the potential benefits. Before such trials should be considered, further preclinical work is needed to demonstrate efficacy of radiotherapy to provide scientific justification for a clinical trial in patients with COVID-19” (28).
Table 1. Data used for re-analysis

| Author          | Ref. | Animal strain           | Infective agent(s)                        | Endpoint(s) analyzed          | Range of dose (Gy) | No of animals | Statistical model used for re-analysis |
|-----------------|------|-------------------------|-------------------------------------------|-------------------------------|--------------------|---------------|----------------------------------------|
| Fried           | (14) | Guinea pig              | *Staphylococcus aureus haemolyticus*      | Improvement in pneumonia morbidity | 0–0.833            | 7             | Exact logistic                          |
| Murphy and Sturm| (12) | White mice              | Type I *Pneumococcus*                     | Mortality                     | NA                 | 75            | Log-linear Cox                         |
| Lieberman et al.| (6)  | Dogs                    | Type I+III *Pneumococcus*                 | Mortality                     | 0.0–4.096          | 45            | Linear + loglinear Cox                 |
| Dubin et al.    | (8)  | White mice              | Swine influenza virus                     | Mortality                     | 0.0–1.754          | 252           | Linear + loglinear Cox                 |
| Baylin et al.   | (7)  | Cats                    | Feline virus (Baker)                      | Degrees of pneumonia          | 0.0–1.754          | 24            | Log logistic + ordinal                 |
| Tanner and McConchie | (24) | CFW mice                | Theilers FA mouse encephalitis virus      | Mortality                     | 0.0–5.262          | 196           | Linear binomial logistic               |
| Hale and Stoner | (19) | Swiss mice              | Influenza type A, *Trichinella spiralis*, type III *Pneumococcus* | Mortality                     | 0.0–6.139          | 658           | Linear binomial logistic               |
| Quilligan et al.| (18) | C57BL male mice         | PR8 strain type A influenza virus          | Mortality                     | 0.0 – 14.471       | 30–34         | Linear binomial logistic               |
| Berlin          | (9)  | CF-1 adult albino male mice | CAM A-prime strain influenza virus       | Morbidity+mortality           | 0.0–3.070          | 362           | Linear binomial logistic               |
| Berlin and Cochran | (10) | CF-1 adult albino male mice | PR8 strain type A influenza virus        | Morbidity+mortality           | 0.0–4.385          | 660           | Linear binomial logistic               |
| Lundgren et al. | (25) | Female C57BL/6J mice    | Type A0 influenza virus                   | Mortality                     | 0.0–166.63         | 364           | Linear binomial logistic               |
Table 2. Improvement in pneumonia morbidity in guinea pigs associated with radiation exposure post inoculation to *Staphylococcus aureus haemolyticus* virus in the data of Fried (14), via fit of a logistic model via exact methods

|                          | ln[EOR] / Gy + 95% CI | p-value |
|--------------------------|-----------------------|---------|
| Only guinea pigs receiving inoculation | 2.42\(^a\) (-0.46\(^b\), +∞\(^b\)) | 0.075   |
| All guinea pigs          | 2.73\(^a\) (-0.08\(^b\), +∞\(^b\)) | 0.057   |

\(^a\)median unbiased estimator

\(^b\)exact 95% CI
Table 3. Risks of death associated with radiation exposure post-inoculation to types I+III *Pneumococcus* in the canine data of Lieberman *et al.* (6) by study group, via fit of a Cox proportional hazards model

| Model     | Group          | ERR / Gy (+95% CI) | p-value |
|-----------|----------------|---------------------|---------|
| Linear    | Group 1        | -0.05 (-0.35, 0.86) | 0.860   |
| Loglinear | Group 1        | -0.05 (-0.58, 0.50) | 0.861   |
| Linear    | Group 2        | -0.37 (-0.41, 0.82) | 0.157   |
| Loglinear | Group 2        | -1.75 (-6.25, 0.27) | 0.096   |
| Linear    | Group 3        | -0.23 (-0.24, -0.16) | <0.001 |
| Loglinear | Group 3        | -0.68 (-1.11, -0.29) | <0.001 |
| Linear    | All groups     | -0.23 (-0.24, -0.16) | <0.001 |
| Loglinear | All groups     | -0.49 (-0.81, -0.19) | <0.001 |
Table 4. Risks of death in mice associated with radiation exposure post inoculation to FA strain mouse encephalitis virus in the data of Tanner and McConchie (24), via fit of a linear logistic model

| EOR / Gy + 95% CI      | p-value |
|------------------------|---------|
| 0.09 (-0.09, 0.61)     | 0.469   |
| Group [pneumonia intensity group contrasts] | ln[OR] / Gy + 95% CI | p-value |
|-------------------------------------------|----------------------|---------|
| **Logistic regression**                   |                      |         |
| Very slight and above vs none             | 21.29 (<-100, >100)  | 0.173   |
| Slight and above vs everything below      | 1.35 (-0.77, 4.77)   | 0.235   |
| Slight to moderate and above vs everything below | 0.92 (-0.42, 2.47) | 0.181   |
| Moderate and above vs everything below    | 0.34 (-1.03, 1.75)   | 0.622   |
| Moderate to marked and above to everything below | -1.35 (-4.77, 0.77) | 0.235   |
| Marked vs everything below                | 0.49 (-3.11, 4.12)   | 0.755   |
| **Ordinal regression**                    |                      |         |
|                                           | 0.55 (-0.62, 1.76)   | 0.358   |
Table 6. Linear regression of days of acute pneumonia infection following feline virus (Baker) inoculation vs post-inoculation radiation dose in data of Baylin et al (7)

| days / Gy + 95% bootstrap CI | BCA Bootstrap p-value |
|-----------------------------|-----------------------|
| -2.56 (-4.59, -0.33)        | 0.015                 |
Table 7. Relative risk of mortality in mice given X-rays after inoculation with type I Pneumococcus of Murphy and Sturm (12) via fit of a Cox proportional hazards model

| Relative risk (hazard ratio) (+ 95% CI) | p-value |
|----------------------------------------|---------|
| X-ray vs not                           | 3.67 (1.84, 7.61) | <0.001 |
Table 8. Risks of death associated with pre- and post-inoculation radiation exposure in white mice inoculated with Swiss influenza virus in data of Dubin et al. (8), evaluated using a Cox proportional hazards model

| Model    | ERR / Gy (+95% CI) | p-value |
|----------|-------------------|---------|
| Linear   | -0.13 (-0.35, 0.27) | 0.451   |
| Loglinear| -0.14 (-0.51, 0.23) | 0.454   |

| Model    | ERR / Gy (+95% CI) | p-value |
|----------|-------------------|---------|
| Linear   | -0.62 (-0.90, -0.09) | 0.029   |
| Loglinear| -0.92 (-1.84, -0.10) | 0.028   |
Table 9. Risks of death in male C57BL mice associated with $^{60}$Co radiation exposure pre-inoculation to intranasally and intraperitoneally administered PR8 strain of type A influenza virus in the data of Quilligan *et al* (18), via fit of a linear-logistic model

|                                                | EOR / Gy + 95% CI | p-value |
|------------------------------------------------|-------------------|---------|
| Assuming 6 mice in first control group         | 3.73 (0.42, 85.85) | <0.001  |
| Assuming 8 mice in first control group         | 4.24 (0.49, 96.97) | <0.001  |
| Assuming 10 mice in first control group        | 4.75 (0.56, 108.10)| <0.001  |
Table 10. Risks of death in Swiss mice associated with pre-inoculation radiation exposure to mixture of influenza virus, *Pneumococcus* type III bacterial infection and larval infection by *Trichinella spiralis* in the data of Hale and Stoner (19), via fit of a linear logistic model

|                                      | EOR / Gy + 95% CI | p-value |
|--------------------------------------|-------------------|---------|
| Unadjusted, all data                 | 0.11 (0.03, 0.21) | 0.004   |
| Unadjusted, fitted to experiments with influenza and *Pneumococcus* challenge infections only | 0.27 (0.13, 0.48) | <0.001 |
| Adjusted for type of challenge infection type<sup>a</sup> | 1.91 (1.12, 3.33) | <0.001 |
| Adjusted for challenge infection type, fitted to experiments with influenza and *Pneumococcus* challenge infections only<sup>a</sup> | 1.71 (0.97, 3.02) | <0.001 |

<sup>a</sup>influenza virus, *Pneumococcus* type III bacterial infection, larval infection by *Trichinella spiralis*
Table 11. Morbidity and mortality risks associated with pre-inoculation radiation exposure in CF-1 adult albino male mice inoculated with CAM A-prime strain of influenza virus in data of Berlin (9) via fit of a linear logistic model.

|                          | EOR / Gy + 95% CI | p-value |
|--------------------------|------------------|---------|
| Pneumonitis morbidity    | -0.24 (-0.28, -0.17) | <0.001  |
| Pneumonitis mortality    | -0.21 (-0.26, -0.14) | <0.001  |
Table 12. Influenza A/PR8 morbidity and mortality risks associated with pre-inoculation radiation exposure in CF-1 adult albino male mice inoculated with CAM A-prime strain of influenza virus in data of Berlin and Cochran (10), evaluated using a linear logistic model

| Table II data – analysis of influenza mortality and morbidity | EOR / Gy + 95% CI | p-value |
|-------------------------------------------------------------|-------------------|---------|
| Influenza morbidity                                         | -0.11 (-0.18, 0.05) | 0.132   |
| Influenza mortality                                         | -0.04 (-0.15, 0.26) | 0.711   |

| Table III data – analysis of influenza mortality considering mode of administration of virus | EOR / Gy + 95% CI | p-value |
|-----------------------------------------------------------------------------------------------|-------------------|---------|
| Unadjusted for mode of administration of influenza virus                                     | 0.21 (0.03, 0.48) | 0.020   |
| Adjusted for mode of administration of influenza virus                                       | 0.25 (0.05, 0.57) | 0.009   |
Table 13. Mortality risks associated with pre-inoculation $^{144}$CeO$_2$ radiation exposure in C57BL/6J mouse inoculated with type A$_0$ influenza virus in data of Lundgren et al (25), evaluated using a linear logistic model

| Mortality  | EOR / Gy + 95% CI          | $p$-value |
|------------|---------------------------|-----------|
|            | 0.008 (0.002, 0.019)      | 0.002     |
Figure 1. Dose response for mortality (+95% CI) in the murine data of Dubin et al. (8) and in the canine data of Lieberman et al. (6)

**Dubin et al (1946) post-inoculation dose**

**Dubin et al (1946) pre-inoculation dose**

**Lieberman et al (1941) post-inoculation dose**
Figure 2. Dose response for mortality (+95% CI) in the canine data of Lieberman et al. (6), by study group.
Figure 3. Days of acute pneumonia infection (+95% CI) vs dose in data of Baylin et al (7)
Figure 4. Mortality in mice (+95% CI) after mouse encephalitis virus and post-inoculation radiation exposure in data of Tanner and McConchie (24)
Figure 5. Influenza morbidity and mortality in mice (+95% CI) after PR8 strain type A influenza virus and pre-inoculation radiation exposure in data of Berlin and Cochran (10)
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