COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

Interim assessment for Synthesis and Integration of Epidemiological and Toxicological Evidence (SETE) for long-term exposure to $PM_{2.5}$ and COVID-19

Working paper for 'Statement on the state of the science linking long-term air pollution exposure with SARS-CoV-2 infection and adverse COVID-19 outcomes'

COMEAP COVID-19 Sub-group – September 2023

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Approach

This description is of an assessment to determine whether there is a causal relationship between long-term exposure to $PM_{2.5}$ and severity of COVID-19 outcomes, following infection with SARS-CoV-2.

COMEAP is trialling this approach to provide a visual representation of the strength of the evidence for causality. This assessment is based on a framework described in a report by the Joint COT and COC Synthesis and Integration of Epidemiological and Toxicological Evidence subgroup (SETE), which aims to review approaches for synthesising and integrating epidemiological and toxicological evidence[1]. COMEAP discussed the application of this framework to its work at the May and November 2022 COMEAP meetings, details of which can be found in the meeting minutes[2]. Discussion points included that it may be more difficult to apply the approach to a complex mixture, such as particulate air pollution, than a well-defined chemical entity. Additionally, COMEAP's approach to integrating epidemiological and toxicological evidence may be different to that used in other chemical risk assessment settings: it was suggested that COMEAP interpreted the axis "epidemiological evidence for causation" as the strength of evidence for an association and the axis "experimental evidence for causation" as the strength of evidence for biological plausibility.

The SETE approach requires that the integration of evidence, and visualisation, is discussed by those evaluating the evidence at each stage of the review process. This SETE assessment has been developed following an evaluation of the evidence as discussed in the statement. The epidemiological and mechanistic evidence reviewed is not comprehensive and, therefore, the assessment of causality should be considered provisional.

Three diagrams are shown that provide a means of visually indicating the consensus view of the Committee on the overall strength of the epidemiological and experimental (mechanistic) evidence for $PM_{2.5}$ causing (i) severe infection, (ii) development of infection, and (iii) mortality. The diagrams are not intended to reflect a probabilistic or numerical approach but instead provide a representation of the influence of the different lines of evidence assessed by in the statement on causation.

[1] SETE | Committee on Toxicity (food.gov.uk)
[2] Minutes of COMEAP meetings are available at: Committee on the Medical Effects of Air Pollutants.

Lines of evidence

Early in the pandemic, some studies suggested that short-term and long-term exposure to air pollution was a risk factor for both infection and severity of COVID-19. However, many of the early studies were either based on correlations or were ecological studies, which did not fully account for other possible explanations for apparent correlations between air pollution and COVID-19.

Cohort studies with individual-level data have generally found associations between long-term previous exposure to $PM_{2.5}$ with COVID-19 hospital admissions and severity of symptoms. Results of studies reporting associations with COVID-19 mortality and SARS-COV2 infection are more mixed. Many of these studies involved cohorts of patients, or individuals with a positive test for COVID-19. Only one study of a purpose-designed cohort is available. Controlling for the potential confounders in studies of air pollution and COVID-19 outcomes is challenging, even in studies with individual-level data.

There is some evidence from experimental studies that exposure to $PM_{2.5}$ pollution can upregulate expression of the cell-surface receptors (ACE2 and TMPRSS2) which allow SARS-CoV-2 to enter cells. Evidence for other respiratory viruses supports the hypothesis that $PM_{2.5}$ exposure may facilitate COVID-19 infection via pathways involving decreased immune response and increased viral entry into cells. Both short-term and long-term exposure to $PM_{2.5}$ may increase SARS-CoV-2 infection and COVID-19 severity and mortality through multiple mechanisms, including increasing the risk of chronic co-morbidities (heart and lung disease) which are known to be risk factors for severe COVID-19 disease.

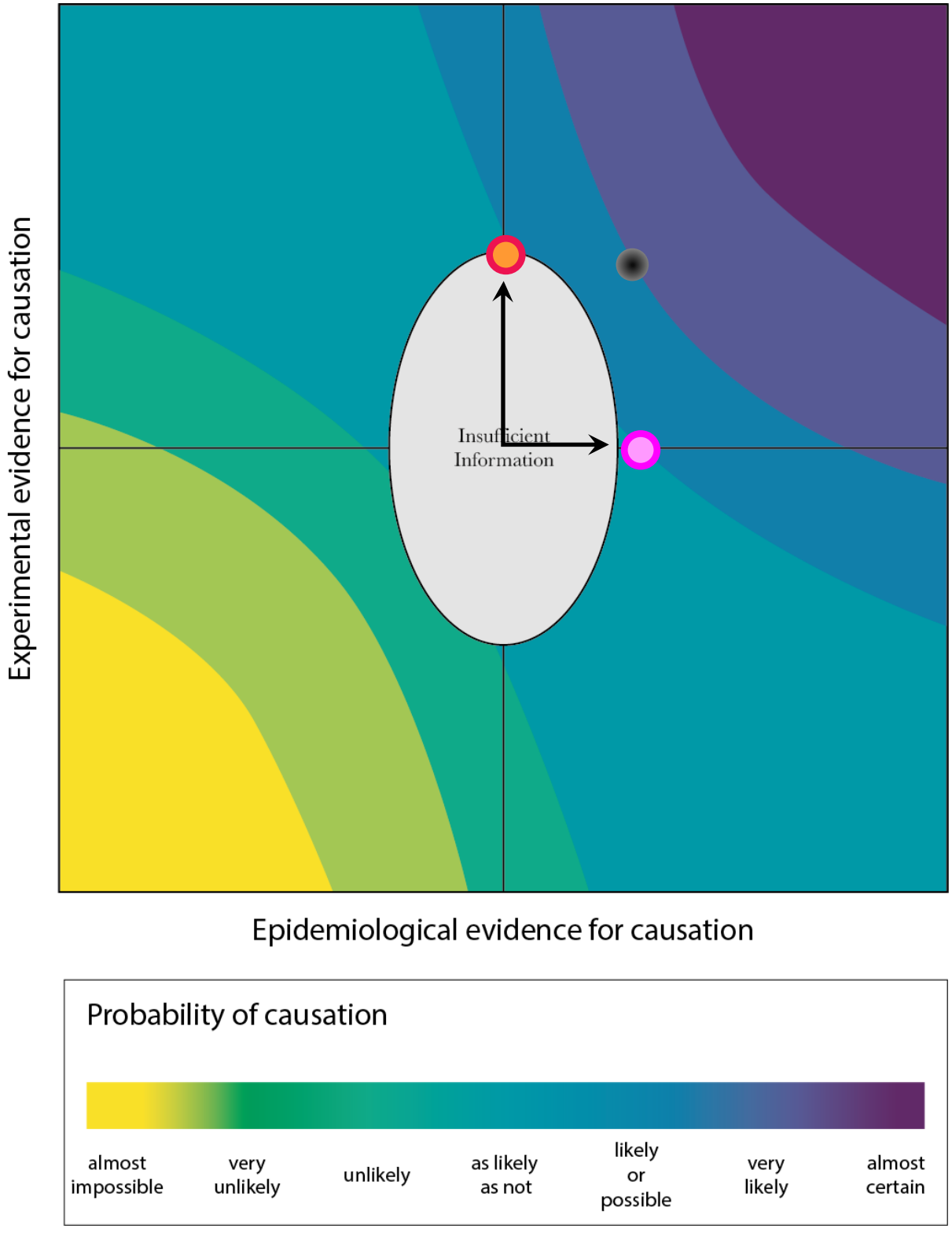
Table 1. Summary of strengths and weaknesses of data examined on long-term exposure to $PM_{2.5}$ and severity of COVID-19 outcomes and influence of lines of evidence on overall conclusion

Lines of evidence and their main strengths (S) and weaknesses (W)	**Influence on conclusion**
<u>Epidemiological data</u> S – Most, though not all, individual-level studies report associations with COVID-19 severity and hospital admissions. W – Results of studies reporting associations with SARS-COV2 infection and COVID-19 mortality are more mixed. W – Many early ecological studies were of poor quality.	There is evidence suggesting that $PM_{2.5}$ increases hospital admissions and susceptibility to more severe COVID-19 outcomes following infection with the SARS-CoV-2 virus. However, the evidence for an association with mortality is more mixed, potentially reducing coherence. The evidence for an association with infection is also mixed, although it is more plausible that the mechanisms might differ from an effect on severity, such that there are less implications for coherence.

W – There are a number of methodological issues which make studies of interactions between air pollution and COVID-19 outcomes difficult to conduct and interpret. In particular, it is not clear to what extent it is possible to adequately adjust for confounders.	
<u>Mechanistic data</u> S – Experimental studies show that exposure to $PM_{2.5}$ increases the expression of the ACE-2 receptor, which is known to allow the virus to attach and enter lung cells. This may increase the viral load and hence severity of disease, as well as likelihood of infection. W – There was no evidence directly demonstrating this mechanism for SARS-CoV-2 at the time of the assessment and it was mainly inferred from studies without exposure to the virus. S – Both short- and long-term exposure to $PM_{2.5}$ can impair innate host defences against respiratory infections, for example: reduced effectiveness of the barrier function of the respiratory tract epithelium, impaired clearance of organisms by the mucociliary escalator, and alterations in the function of alveolar macrophages. S – Exposure to air pollutants is associated with increased risk of hospital admissions for respiratory diseases, suggesting biological plausibility. W – Most evidence of associations with other respiratory infections relates to short-term exposures to air pollutants. Evidence for increased risk of developing chronic respiratory disease following long-term exposure is weaker than for hospital admissions associated with short-term elevations.	There is evidence to support plausible mechanisms by which air pollutants could affect COVID-19 outcomes. Most of the relevant evidence is indirect.

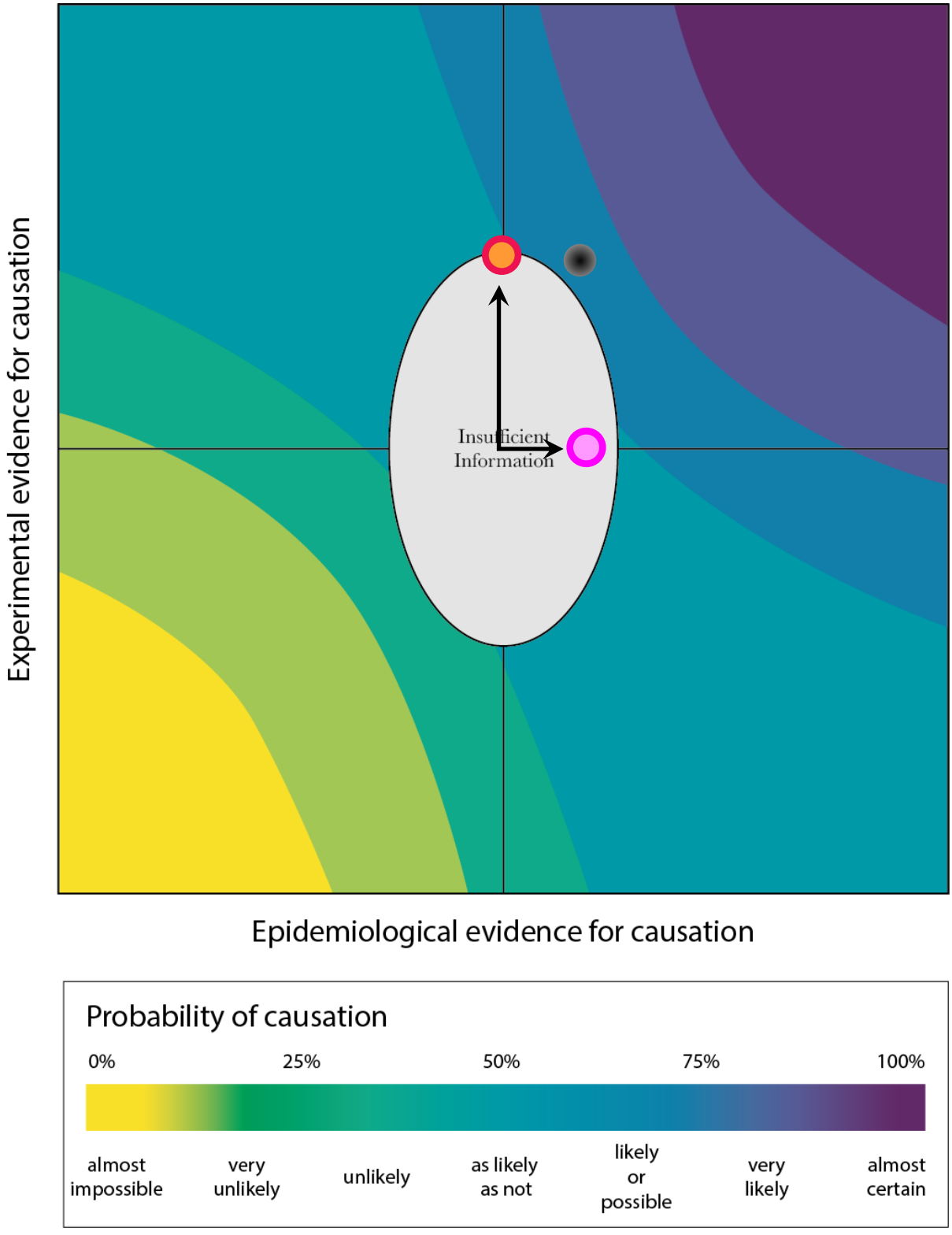
S – The established links between long-term exposure to $PM_{2.5}$ and heart and lung disease suggest that it could make individuals more susceptible to severe COVID-19 symptoms, as individuals with these conditions are at greater risk of severe COVID-19. S – $PM_{2.5}$ affects trained immunity in innate immune cells, making subsequent inflammatory responses to stimuli more severe. An extreme inflammatory response is involved in severe COVID-19. S – $PM_{2.5}$ and COVID-19 infection both affect the vasculature and blood in similar ways, making blood clots more likely. The effect of increased clotting contributes to an increased risk of hospitalisation and mortality from cardiovascular disease. W – although effects of long-term exposure seem likely, most of the experimental mechanistic evidence of effects of air pollution on cardiovascular indices relates to short-term exposure.	
<u>Conclusions on causality</u>	The available studies on COVID-19, together with evidence of effects of respiratory infections more generally, suggest that long-term exposure to $PM_{2.5}$ is more than likely to increase the risk of more severe symptoms of COVID-19. The epidemiological evidence for the effects of long-term exposure to $PM_{2.5}$ increasing the risk of infectivity and mortality is more mixed. There is also a lack of direct mechanistic evidence of $PM_{2.5}$ mediated effects inducing increased COVID-19 infectivity and mortality, Therefore, it is concluded that associations between $PM_{2.5}$ and the risk of developing infections, and $PM_{2.5}$ and the risk of mortality, are possible but more evidence would be needed to infer causality.

Figure 1. Interim assessment and visualisation of causality of long-term exposure to $PM_{2.5}$ and severe COVID-19 or hospitalisation



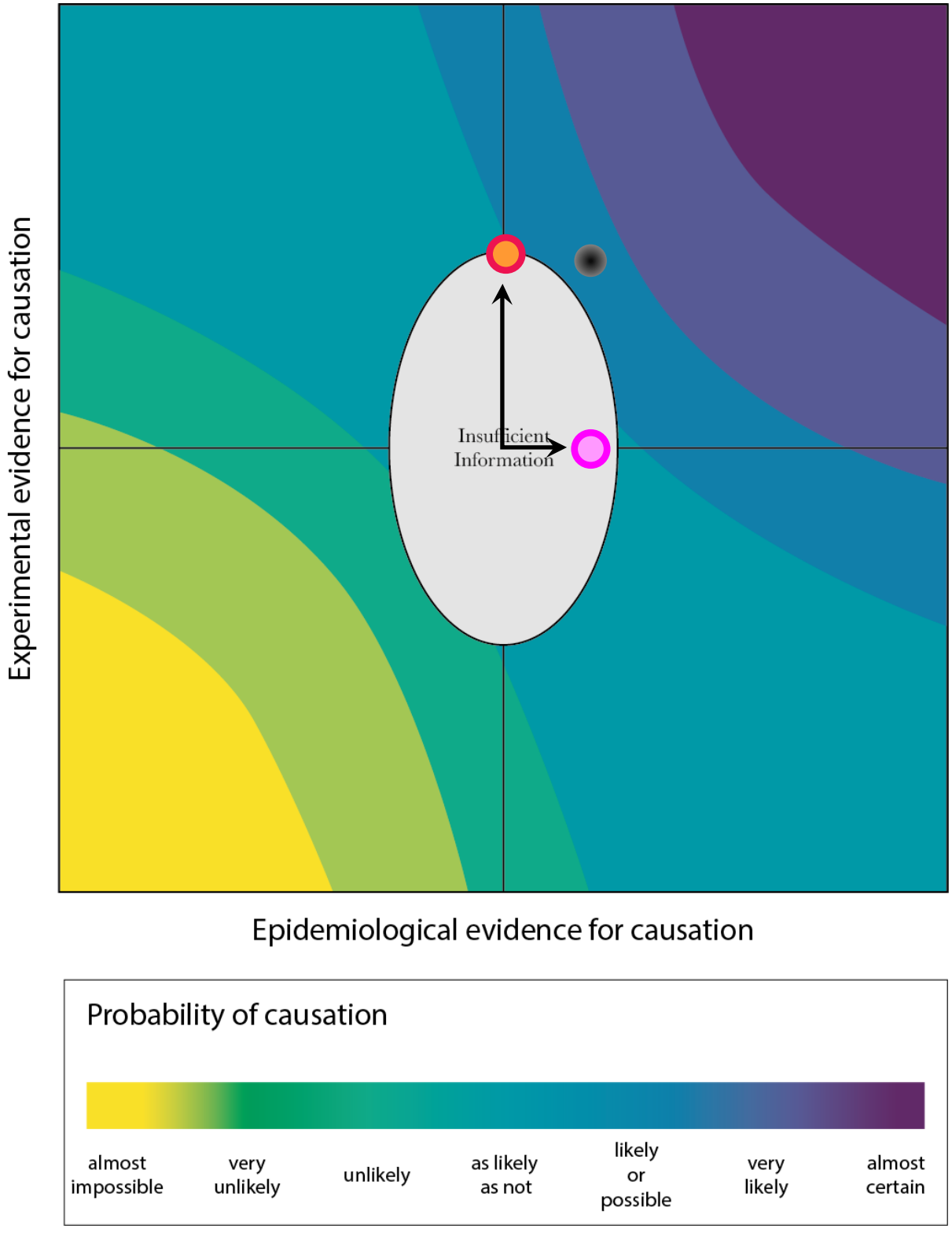
The pink circle is representative of all epidemiological evidence assessed; the orange circle of all toxicological evidence assessed. The black circle represents the conclusion of causality of the integrated evidence: between “likely or possible” and “very likely”.

Figure 2. Interim assessment and visualisation of causality of long-term exposure to $PM_{2.5}$ and developing infection from SARS-CoV-2



The pink circle is representative of all epidemiological evidence assessed; the orange circle of all toxicological evidence assessed. The black circle represents the conclusion of causality of the integrated evidence: “likely or possible”.

Figure 3. Interim assessment and visualisation of causality of long-term exposure to $PM_{2.5}$ and mortality from COVID-19



The pink circle is representative of all epidemiological evidence assessed; the orange circle of all toxicological evidence assessed. The black circle represents the conclusion of causality of the integrated evidence: “likely or possible”.