

**Journal:** European Journal of Epidemiology

**Title:** Seasonal and pandemic influenza during pregnancy and risk of fetal death: A Norwegian registry-based cohort study

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## Fetal Death in the Second Trimester with Seasonal and Pandemic Influenza

|         | Number of birth records      | Number of fetal deaths <sup>1</sup> | Crude HR (95% CI) | Adjusted HR (95% CI) <sup>2</sup> |  |
|---------|------------------------------|-------------------------------------|-------------------|-----------------------------------|--|
| Total   | 417,400                      | 1,460                               | —                 | —                                 |  |
| Model 1 | <i>Seasonal influenza</i>    |                                     |                   |                                   |  |
|         | No                           | 414,228                             | 1                 | 1                                 |  |
|         | Yes                          | 6,621                               | 0.91 (0.56–1.49)  | 0.93 (0.57–1.52)                  |  |
|         | <i>Pandemic influenza</i>    |                                     |                   |                                   |  |
|         | No                           | 415,924                             | 1                 | 1                                 |  |
|         | Yes                          | 2,870                               | 2.03 (1.24–3.32)  | 2.11 (1.29–3.46)                  |  |
| Model 2 | <i>Seasonal influenza</i>    |                                     |                   |                                   |  |
|         | No                           | 414,228                             | 1                 | 1                                 |  |
|         | Yes, in the first trimester  | 3,051                               | 1.22 (0.71–2.10)  | 1.24 (0.72–2.14)                  |  |
|         | Yes, in the second trimester | 3,570                               | 0.44 (0.14–1.35)  | 0.45 (0.14–1.39)                  |  |
|         | <i>Pandemic influenza</i>    |                                     |                   |                                   |  |
|         | No                           | 415,924                             | 1                 | 1                                 |  |
|         | Yes, in the first trimester  | 1,406                               | 2.26 (1.25–4.08)  | 2.28 (1.26–4.13)                  |  |
|         | Yes, in the second trimester | 1,464                               | 1.65 (0.69–3.98)  | 1.80 (0.75–4.33)                  |  |

<sup>1</sup>Spontaneous abortions (miscarriages) and stillbirths.

<sup>2</sup>Adjustment for maternal age, maternal marital status, maternal parity, maternal history of fetal death, maternal chronic conditions (asthma, chronic hypertension, chronic renal disease, rheumatoid arthritis, heart disease, epilepsy, diabetes, or thyroid disease), maternal use of nutritional supplements before and/or during pregnancy, and maternal smoking at the beginning of pregnancy as baseline covariates and calendar season and maternal seasonal/pandemic influenza as time-dependent covariates.

**Supplementary Fig. 1** Hazard ratios (HRs) of fetal death in the second trimester, with associated 95% confidence intervals (CIs), between women with and without a diagnosis of influenza-like illness in pregnancy during regular influenza seasons (seasonal influenza) and with and without a diagnosis of influenza-like illness in pregnancy during the 2009/2010 pandemic season (pandemic influenza), respectively. Estimated by using Cox proportional-hazards regression with follow-up between January 1, 2006, and December 31, 2013. Adjusted HRs also displayed graphically to the far right

## Fetal Death in the Third Trimester with Seasonal and Pandemic Influenza

|         | Number of birth records               | Number of fetal deaths <sup>1</sup> | Crude HR (95% CI) | Adjusted HR (95% CI) <sup>2</sup> |  |
|---------|---------------------------------------|-------------------------------------|-------------------|-----------------------------------|--|
| Total   | 414,972                               | 1,040                               | —                 | —                                 |  |
| Model 1 | <i>Seasonal influenza</i>             |                                     |                   |                                   |  |
|         | No                                    | 408,334                             | 1                 | 1                                 |  |
|         | Yes                                   | 8,307                               | 0.86 (0.53–1.39)  | 0.89 (0.55–1.43)                  |  |
|         | <i>Pandemic influenza</i>             |                                     |                   |                                   |  |
|         | No                                    | 412,099                             | 1                 | 1                                 |  |
|         | Yes                                   | 3,559                               | 1.42 (0.80–2.51)  | 1.44 (0.82–2.55)                  |  |
| Model 2 | <i>Seasonal influenza</i>             |                                     |                   |                                   |  |
|         | No                                    | 408,334                             | 1                 | 1                                 |  |
|         | Yes, in the first trimester           | 3,027                               | 0.93 (0.44–1.97)  | 0.97 (0.46–2.05)                  |  |
|         | Yes, in the second or third trimester | 5,280                               | 0.82 (0.44–1.52)  | 0.84 (0.45–1.57)                  |  |
|         | <i>Pandemic influenza</i>             |                                     |                   |                                   |  |
|         | No                                    | 412,099                             | 1                 | 1                                 |  |
|         | Yes, in the first trimester           | 1,394                               | 2.28 (1.14–4.57)  | 2.34 (1.17–4.69)                  |  |
|         | Yes, in the second or third trimester | 2,165                               | 0.81 (0.30–2.16)  | 0.81 (0.30–2.17)                  |  |

<sup>1</sup>Spontaneous abortions (miscarriages) and stillbirths.

<sup>2</sup>Adjustment for maternal age, maternal marital status, maternal parity, maternal history of fetal death, maternal chronic conditions (asthma, chronic hypertension, chronic renal disease, rheumatoid arthritis, heart disease, epilepsy, diabetes, or thyroid disease), maternal use of nutritional supplements before and/or during pregnancy, and maternal smoking at the beginning of pregnancy as baseline covariates and calendar season and maternal seasonal/pandemic influenza as time-dependent covariates.

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**Supplementary Fig. 2** Hazard ratios (HRs) of fetal death in the third trimester, with associated 95% confidence intervals (CIs), between women with and without a diagnosis of influenza-like illness in pregnancy during regular influenza seasons (seasonal influenza) and with and without a diagnosis of influenza-like illness in pregnancy during the 2009/2010 pandemic season (pandemic influenza), respectively. Estimated by using Cox proportional-hazards regression with follow-up between January 1, 2006, and December 31, 2013. Adjusted HRs also displayed graphically to the far right

## Fetal Death after the First Trimester with Pandemic Influenza and Vaccination

|         | Number of birth records               | Number of fetal deaths <sup>1</sup> | Crude HR (95% CI) | Adjusted HR (95% CI) <sup>2</sup> |  |
|---------|---------------------------------------|-------------------------------------|-------------------|-----------------------------------|--|
| Total   | 113,135                               | 451                                 | —                 | —                                 |  |
| Model 3 | <i>Pandemic influenza</i>             |                                     |                   |                                   |  |
|         | No                                    | 111,493                             | 1                 | 1                                 |  |
|         | Yes                                   | 3,578                               | 1.85 (1.25–2.74)  | 1.84 (1.23–2.73)                  |  |
|         | <i>Pandemic vaccination</i>           |                                     |                   |                                   |  |
|         | No                                    | 108,441                             | 1                 | 1                                 |  |
|         | Yes                                   | 26,303                              | 0.94 (0.74–1.20)  | 0.86 (0.66–1.12)                  |  |
| Model 4 | <i>Pandemic influenza</i>             |                                     |                   |                                   |  |
|         | No                                    | 111,493                             | 1                 | 1                                 |  |
|         | Yes, in the first trimester           | 1,405                               | 2.44 (1.52–3.91)  | 2.40 (1.49–3.87)                  |  |
|         | Yes, in the second or third trimester | 2,173                               | 1.25 (0.64–2.42)  | 1.24 (0.64–2.41)                  |  |
|         | <i>Pandemic vaccination</i>           |                                     |                   |                                   |  |
|         | No                                    | 108,441                             | 1                 | 1                                 |  |
|         | Yes, in the first trimester           | 2,465                               | 0.88 (0.50–1.57)  | 0.86 (0.48–1.53)                  |  |
|         | Yes, in the second or third trimester | 23,838                              | 0.95 (0.74–1.23)  | 0.86 (0.65–1.14)                  |  |

<sup>1</sup>Spontaneous abortions (miscarriages) and stillbirths.

<sup>2</sup>Adjustment for maternal age, maternal marital status, maternal parity, maternal history of fetal death, maternal chronic conditions (asthma, chronic hypertension, chronic renal disease, rheumatoid arthritis, heart disease, epilepsy, diabetes, or thyroid disease), maternal use of nutritional supplements before and/or during pregnancy, and maternal smoking at the beginning of pregnancy as baseline covariates and calendar season and maternal pandemic influenza/vaccination as time-dependent covariates.

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**Supplementary Fig. 3** Hazard ratios (HRs) of fetal death in the second or third trimester, with associated 95% confidence intervals (CIs), between women with and without a diagnosis of influenza-like illness in pregnancy during the 2009/2010 pandemic season (pandemic influenza) and with and without vaccination against pandemic influenza virus in pregnancy (pandemic vaccination), respectively. Estimated by using Cox proportional-hazards regression with follow-up between May 15, 2009, and September 30, 2010. Adjusted HRs also displayed graphically to the far right

## Fetal Death in the Second Trimester with Pandemic Influenza and Vaccination

|         | Number of birth records      | Number of fetal deaths <sup>1</sup> | Crude HR (95% CI) | Adjusted HR (95% CI) <sup>2</sup> |  |
|---------|------------------------------|-------------------------------------|-------------------|-----------------------------------|--|
| Total   | 98,774                       | 261                                 | —                 | —                                 |  |
| Model 3 | <i>Pandemic influenza</i>    |                                     |                   |                                   |  |
|         | No                           | 97,132                              | 1                 | 1                                 |  |
|         | Yes                          | 2,869                               | 2.24 (1.35–3.73)  | 2.09 (1.25–3.51)                  |  |
|         | <i>Pandemic vaccination</i>  |                                     |                   |                                   |  |
|         | No                           | 94,080                              | 1                 | 1                                 |  |
|         | Yes                          | 17,414                              | 1.14 (0.81–1.59)  | 0.98 (0.68–1.42)                  |  |
| Model 4 | <i>Pandemic influenza</i>    |                                     |                   |                                   |  |
|         | No                           | 97,132                              | 1                 | 1                                 |  |
|         | Yes, in the first trimester  | 1,405                               | 2.52 (1.37–4.61)  | 2.35 (1.28–4.32)                  |  |
|         | Yes, in the second trimester | 1,464                               | 1.81 (0.75–4.38)  | 1.67 (0.69–4.06)                  |  |
|         | <i>Pandemic vaccination</i>  |                                     |                   |                                   |  |
|         | No                           | 94,080                              | 1                 | 1                                 |  |
|         | Yes, in the first trimester  | 2,465                               | 0.77 (0.34–1.73)  | 0.74 (0.33–1.66)                  |  |
|         | Yes, in the second trimester | 14,949                              | 1.24 (0.87–1.78)  | 1.06 (0.70–1.61)                  |  |

<sup>1</sup>Spontaneous abortions (miscarriages) and stillbirths.

<sup>2</sup>Adjustment for maternal age, maternal marital status, maternal parity, maternal history of fetal death, maternal chronic conditions (asthma, chronic hypertension, chronic renal disease, rheumatoid arthritis, heart disease, epilepsy, diabetes, or thyroid disease), maternal use of nutritional supplements before and/or during pregnancy, and maternal smoking at the beginning of pregnancy as baseline covariates and calendar season and maternal pandemic influenza/vaccination as time-dependent covariates.

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**Supplementary Fig. 4** Hazard ratios (HRs) of fetal death in the second trimester, with associated 95% confidence intervals (CIs), between women with and without a diagnosis of influenza-like illness in pregnancy during the 2009/2010 pandemic season (pandemic influenza) and with and without vaccination against pandemic influenza virus in pregnancy (pandemic vaccination), respectively. Estimated by using Cox proportional-hazards regression with follow-up between May 15, 2009, and September 30, 2010. Adjusted HRs also displayed graphically to the far right

## Fetal Death in the Third Trimester with Pandemic Influenza and Vaccination

|         | Number of birth records               | Number of fetal deaths <sup>1</sup> | Crude HR (95% CI) | Adjusted HR (95% CI) <sup>2</sup> |  |
|---------|---------------------------------------|-------------------------------------|-------------------|-----------------------------------|--|
| Total   | 95,085                                | 187                                 | —                 | —                                 |  |
| Model 3 | <i>Pandemic influenza</i>             |                                     |                   |                                   |  |
|         | No                                    | 92,221                              | 1                 | 1                                 |  |
|         | Yes                                   | 3,542                               | 1.50 (0.81–2.75)  | 1.49 (0.80–2.76)                  |  |
|         | <i>Pandemic vaccination</i>           |                                     |                   |                                   |  |
|         | No                                    | 77,401                              | 1                 | 1                                 |  |
|         | Yes                                   | 26,230                              | 0.79 (0.57–1.10)  | 0.69 (0.47–1.03)                  |  |
| Model 4 | <i>Pandemic influenza</i>             |                                     |                   |                                   |  |
|         | No                                    | 92,221                              | 1                 | 1                                 |  |
|         | Yes, in the first trimester           | 1,377                               | 2.37 (1.12–5.05)  | 2.26 (1.06–4.81)                  |  |
|         | Yes, in the second or third trimester | 2,165                               | 0.91 (0.34–2.45)  | 0.92 (0.34–2.50)                  |  |
|         | <i>Pandemic vaccination</i>           |                                     |                   |                                   |  |
|         | No                                    | 77,401                              | 1                 | 1                                 |  |
|         | Yes, in the first trimester           | 2,453                               | 1.04 (0.46–2.36)  | 1.05 (0.46–2.39)                  |  |
|         | Yes, in the second or third trimester | 23,777                              | 0.76 (0.54–1.08)  | 0.64 (0.42–0.96)                  |  |

<sup>1</sup>Spontaneous abortions (miscarriages) and stillbirths.

<sup>2</sup>Adjustment for maternal age, maternal marital status, maternal parity, maternal history of fetal death, maternal chronic conditions (asthma, chronic hypertension, chronic renal disease, rheumatoid arthritis, heart disease, epilepsy, diabetes, or thyroid disease), maternal use of nutritional supplements before and/or during pregnancy, and maternal smoking at the beginning of pregnancy as baseline covariates and calendar season and maternal pandemic influenza/vaccination as time-dependent covariates.

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**Supplementary Fig. 5** Hazard ratios (HRs) of fetal death in the third trimester, with associated 95% confidence intervals (CIs), between women with and without a diagnosis of influenza-like illness in pregnancy during the 2009/2010 pandemic season (pandemic influenza) and with and without vaccination against pandemic influenza virus in pregnancy (pandemic vaccination), respectively. Estimated by using Cox proportional-hazards regression with follow-up between May 15, 2009, and September 30, 2010. Adjusted HRs also displayed graphically to the far right