Research questions

| Question number | 1 | | | | | | Notes |
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| Date of consideration | 5 October 2017 | | | | | | |
| New Question (in full) | In Rh D negative pregnant women with no preformed anti-D, does universal[[1]](#footnote-1) routine antenatal prophylaxis with Rh D immunoglobulin (1 or 2 doses) prevent Rh D alloimmunisation? | | | | | | |
| Subquestions (in full) | In Rh D negative pregnant women with no preformed anti-D, is universal routine antenatal prophylaxis with one dose of Rh D immunoglobulin as effective at preventing Rh D alloimmunisation as universal routine prophylaxis with two doses of Rh D immunoglobulin? | | | | | | The evidence for this question will come from the same evidence base as identified for the above question – so it is included as a subquestion rather than a separate question |
| Question type | Population | Intervention | | | Comparator | Outcome | Importance of outcome[[2]](#footnote-2) |
| Main Question  (Intervention) | Rh D negative pregnant women with no preformed anti-D | Routine antenatal prophylactic Rh D immunoglobulin  Stratify by:   * 1 or 2 doses * 1 dose only * 2 doses only | | | Placebo or no routine antenatal prophylactic Rh D immunoglobulin | * incidence of Rh D alloimmunisation[[3]](#footnote-3) * incidence of a positive test for feto-maternal haemorrhage[[4]](#footnote-4) (e.g. Kleihauer test, flow cytometry) * adverse neonatal events (e.g. jaundice) * adverse maternal events attributed to anti-D (e.g. allergic response, infection) | Critical  Not Important  If available[[5]](#footnote-5)  If availablee |
| Subquestion  (Intervention) | Rh D negative pregnant women with no preformed anti-D | 1-dose routine antenatal prophylactic Rh D immunoglobulin | | | 2-dose routine antenatal prophylactic Rh D immunoglobulin | * incidence of Rh D alloimmunisation * adverse neonatal events (e.g. jaundice) * adverse maternal events (e.g. allergic response, infection) | Critical  If availablee  If availablee |
| Additional information | | | | | | | |
| Data to extract | Number of pregnancies | | Product type  Mode of administration  Number of doses  Dosage  Timing | Subquestion only  Product type  Mode of administration  Dosage  Timing | | Rh D alloimmunisation  Timing (i.e., during pregnancy, postpartum [after birth of a Rh-positive infant up to 12 months] and subsequent pregnancy)  Kleihauer test / flow cytometry  At potentially sensitising events and postpartum [after birth of a Rh-positive infant])  Adverse neonatal events  Timing (current or subsequent pregnancy) and severity  Adverse maternal events  Timing and severity |  |

Source: Anti-D scoping report (Health Research Consulting, November 2017)

| Question number | 2 | | | | | | Notes |
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| Date of consideration | 05 October 2017 | | | | | | |
| New Question (in full) | In Rh D negative women with no preformed anti-D who have experienced one of the following first trimester[[6]](#footnote-6) sensitising events – abdominal trauma, molar pregnancy, ectopic pregnancy, spontaneous miscarriage, threatened miscarriage or medical termination of pregnancy (with/without a curette), does universal[[7]](#footnote-7) first-trimester sensitising event prophylaxis with Rh D immunoglobulin prevent Rh D alloimmunisation? | | | | | | |
| Subquestions (in full) | -- | | | | | | |
| Question type | Population | Intervention | | Comparator | | Outcome | Importance of outcome[[8]](#footnote-8) |
| Main Question  (intervention) | Rh D negative women with no preformed anti-D with a first-trimester sensitising event, specifically:   * abdominal trauma * molar pregnancy * ectopic pregnancy * spontaneous miscarriage * threatened miscarriage * medical termination of pregnancy (with/without a curette) | First trimester sensitising event prophylactic Rh D immunoglobulin | | Placebo or no first trimester sensitising event prophylactic Rh D immunoglobulin | | * incidence of Rh D alloimmunisation[[9]](#footnote-9) * incidence of a positive test for feto-maternal haemorrhage[[10]](#footnote-10) (e.g. (Kleihauer test, flow cytometry) * adverse neonatal events (e.g. jaundice) * adverse maternal events attributed to anti-D (e.g. allergic response, infection) | Critical  Not important  If available[[11]](#footnote-11)  If availablek |
| Additional information | | | | | | | |
| Data to extract | Number of pregnancies  Timing of sensitising event  Nature of sensitising event  Use of curette | | Product type  Mode of administration  Number of doses  Dosage  Timing | |  | Rh D alloimmunisation  Timing (i.e., during pregnancy, postpartum [after birth of a Rh-positive infant up to 12 months] and subsequent pregnancy)  Kleihauer test / flow cytometry  At potentially sensitising events and postpartum [after birth of a Rh-positive infant])  Adverse neonatal events  Timing (current or subsequent pregnancy) and severity  Adverse maternal events  Timing and severity |  |

Source: Anti-D scoping report (Health Research Consulting, November 2017)

| Question number | 3 | | | | | | Notes |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Date of consideration | 05 October 2017 | | | | | | |
| New Question (in full) | In Rh D negative pregnant women with no preformed anti-D, does targeted[[12]](#footnote-12) routine antenatal or sensitising event prophylaxis to women with a Rh D positive fetus increase the incidence of Rh D alloimmunisation compared with universal[[13]](#footnote-13) routine antenatal or sensitising event prophylaxis? | | | | | | |
| Subquestions (in full) | In Rh D negative pregnant women with no preformed anti-D, what is the diagnostic accuracy of noninvasive prenatal screening to identify fetal Rh D status? | | | | | |  |
| Question type | Population | Intervention/Test | | Comparator and/or reference standard | | Outcome | Importance of outcome[[14]](#footnote-14) |
| Main Question  (Screening) | Rh D negative pregnant women with no preformed anti-D | Targeted administration of prophylactic Rh D immunoglobulin (based on noninvasive prenatal screening)  Stratify by:   * any prophylaxis * routine antenatal prophylaxis * sensitising event antenatal prophylaxis | | Universal administration of prophylactic Rh D immunoglobulin  Stratify by:   * any prophylaxis * routine antenatal prophylaxis * sensitising event antenatal prophylaxis | | * incidence of Rh D alloimmunisation[[15]](#footnote-15) * utilisation of anti-D * incidence of a positive test for feto-maternal haemorrhage[[16]](#footnote-16) (e.g. Kleihauer test, flow cytometry) * adverse neonatal events (e.g. jaundice) * adverse maternal events attributed to anti-D (e.g. allergic response, infection) | Critical  Resource use  Not important  If available[[17]](#footnote-17)  If availablef |
| Subquestion  (Diagnostic) | Rh D negative pregnant women with no preformed anti-D | Noninvasive prenatal testing for fetal Rh D status | | Postnatal cord blood testing (or other neonatal sample) for fetal Rh D status  Other noninvasive fetal RhD determination | | * sensitivity * specificity * false positives * false negatives * positive likelihood ratio * negative likelihood ratio | Critical  Critical  Critical  Critical  Important  Important |
| Additional information | | | | | | | |
| Data to extract | Number of pregnancies  BMI | | Screening question  Product type  Number of doses  Dosage  Timing  Testing methodology  Timing  Diagnostic question  Testing methodology  Timing | | Screening question  Product type  Number of doses  Dosage  Timing  Diagnostic question  Testing methodology  Timing | Rh D alloimmunisation  Timing (i.e., during pregnancy, postpartum [after birth of a Rh-positive infant up to 12 months] and subsequent pregnancy)  Utilisation  Rates  Kleihauer test /flow cytometry  At potentially sensitising events and postpartum [after birth of a Rh-positive infant])  Adverse neonatal events  Timing (current or subsequent pregnancy) and severity  Adverse maternal events  Timing and severity  Diagnostic accuracy  Timing of test |  |

Source: Anti-D scoping report (Health Research Consulting, November 2017)

| Question number | 4 | | | Notes |
| --- | --- | --- | --- | --- |
| Date of consideration | 05 October 2017 | | | |
| New Question (in full) | In Rh D negative pregnant or postpartum women with no preformed anti-D, does increasing BMI increase the risk of failure of anti-D administration? | | | |
| Subquestions (in full) | -- | | | |
| Question type | Population | Prognostic/Risk factor | Outcome | Importance of outcome[[18]](#footnote-18) |
| Main Question  (prognostic) | Rh D negative pregnant or postpartum women with no preformed anti-D receiving prophylactic Rh D immunoglobulin  Stratify by   * pregnant women * postpartum women | * BMI (dichotomous or continuous) * weight * any other weight-related factors examined | * incidence of Rh D alloimmunisation[[19]](#footnote-19) * anti-D levels [[20]](#footnote-20) * incidence of a positive test for feto-maternal haemorrhage (e.g. (Kleihauer test, flow cytometry)[[21]](#footnote-21) * adverse neonatal events (e.g. jaundice) * adverse maternal events (e.g. allergic response, infection) | Critical  Critical (if data for Rh D alloimmunisation is not available)  Not important  If available  If available (particularly if increased dose or different mode of administration/technique used) |
| Additional information | | | | |
| Data to extract | Product type  Mode of administration  Number of doses/dosage  Timing of administration  Administration technique | Specific details of weight-related risk factors | Rh D alloimmunisation  Timing (i.e., during pregnancy, postpartum [after birth of a Rh-positive infant] up to 12 months and subsequent pregnancy)  Anti-D levels  Timing  Kleihauer test /flow cytometry  At potentially sensitising events and postpartum [after birth of a Rh-positive infant])  Adverse neonatal events  Timing (current or subsequent pregnancy) and severity  Adverse maternal events  Timing and severity |  |

Source: Anti-D scoping report (Health Research Consulting, November 2017)

1. Includes all pregnant women who are Rh D negative with no preformed anti-D. [↑](#footnote-ref-1)
2. Critical, important or resource use. [↑](#footnote-ref-2)
3. Also known as Rh D sensitisation. Defined as the presence of antibody to D antigen in maternal serum detected during the current pregnancy, postpartum or a subsequent pregnancy. Measured as a dichotomous outcome (present or not present). [↑](#footnote-ref-3)
4. The ERG debated whether to include ‘incidence of a positive Kleihauer test’ as an outcome. Given its inclusion in the 2015 Cochrane review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000020.pub3/full) the ERG agreed to include in this review, but have noted the outcome as not important. [↑](#footnote-ref-4)
5. Data will be extracted for these outcomes if they are available in the studies included for the critical outcome – Rh D alloimmunisation. Additional searches to identify studies for these outcomes will not be conducted. [↑](#footnote-ref-5)
6. The definition of first trimester varies across countries and for this review will be defined by the literature. The definition used by each included study should be extracted. [↑](#footnote-ref-6)
7. Includes all pregnant women who are Rh D negative with no preformed anti-D. [↑](#footnote-ref-7)
8. Critical, important or resource use. [↑](#footnote-ref-8)
9. Also known as Rh D sensitisation. Defined as the presence of antibody to D antigen in maternal serum detected during the current pregnancy, postpartum or a subsequent pregnancy. Measured as a dichotomous outcome (present or not present). [↑](#footnote-ref-9)
10. The ERG debated whether to include ‘incidence of a positive Kleihauer test’ as an outcome. Given its inclusion in the 2015 Cochrane review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000020.pub3/full) the ERG agreed to include in this review, but have noted the outcome as not important. [↑](#footnote-ref-10)
11. Data will be extracted for these outcomes if they are available in the studies included for the critical outcome – Rh D alloimmunisation. Additional searches to identify studies for these outcomes will not be conducted. [↑](#footnote-ref-11)
12. Includes pregnant women who are Rh D negative with no preformed anti-D with a Rh D positive fetus identified via first trimester non-invasive prenatal screening. [↑](#footnote-ref-12)
13. Includes all pregnant women who are Rh D negative with no preformed anti-D. [↑](#footnote-ref-13)
14. Critical, important or resource use. [↑](#footnote-ref-14)
15. Also known as Rh D sensitisation. Defined as the presence of antibody to D antigen in maternal serum detected during the current pregnancy, postpartum or a subsequent pregnancy. Measured as a dichotomous outcome (present or not present). [↑](#footnote-ref-15)
16. The ERG debated whether to include ‘incidence of a positive Kleihauer test’ as an outcome. Given its inclusion in the 2015 Cochrane review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000020.pub3/full), the ERG agreed to include in this review, but have noted the outcome as not important. [↑](#footnote-ref-16)
17. Data will be extracted for these outcomes if they are available in the studies included for the critical outcome – Rh D alloimmunisation. Additional searches to identify studies for these outcomes will not be conducted. [↑](#footnote-ref-17)
18. Critical, important or resource use. [↑](#footnote-ref-18)
19. Also known as Rh D sensitisation. Defined as the presence of antibody to D antigen in maternal serum detected during the current pregnancy, postpartum or a subsequent pregnancy. Measured as a dichotomous outcome (present or not present). [↑](#footnote-ref-19)
20. This is a surrogate outcome. Measured as a continuous outcome (actual anti-D level in maternal blood). If this is used instead of Rh D alloimmunisation will need background research to look for evidence of link between lower anti-D levels and alloimmunisation. [↑](#footnote-ref-20)
21. The ERG debated whether to include ‘incidence of a positive Kleihauer test’ as an outcome. Given its inclusion in the 2015 Cochrane review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000020.pub3/full), the ERG agreed to include in this review, but have noted the outcome as not important. [↑](#footnote-ref-21)