Full application for an addition of a test categories in the EDL

Survey response 1

Response ID
82

Date submitted
1980-01-01 00:00:00

Last page
1

Start language
en

1. Name of test category

Name of the test category addressed in the original submission:
Rubella IgG Test

2. Pre-submission information

Please indicate your pre-submission response ID: [Pre-submission ID]
205

3. Applicant’s information (primary contact person):

Contact person, name and information of the person submitting the application: [LAST NAME, First name]
MULDERS, Mick

Contact person, name and information of the person submitting the application: [Email address (...@....)]
muldersm@who.int

Contact person, name and information of the person submitting the application: [Phone number (+country code) phone number no spaces]
+41 22 791-5462

Contact person, name and information of the person submitting the application: [Other information]
Scientist

4. Applicant’s information (secondary contact person):

[LAST NAME, First name]

[Email address (...@....)]

[Phone number (+country code) phone number no spaces]

[Other information]

5. Details of the organization making the submission (if applicable)

Name of the organization making the submission (if applicable): [Name of the organisation]

Name of the organization making the submission (if applicable): [Address]

Name of the organization making the submission (if applicable): [Department]

Name of the organization making the submission (if applicable): [Website]

Name of the organization making the submission (if applicable): [Phone number]

6. Details of the organizations supporting the application:

Please provide up to three organizations supporting your application including a. Organization name, b. Contact person, c. Email address:

7. Public health impact of the disease/condition:

Please detail the public health relevance of conditions addressed with the proposed test and add references:
Rubella is a virally transmitted contagious infectious disease that affects unvaccinated children and young adults. The virus is easily transmitted by respiratory droplets from an infected individual. Childhood infection is often mild and resolves without complication. However, if an unvaccinated woman gets rubella in early pregnancy, serious consequences can result, including miscarriages, fetal deaths, still-births, and having infants born with congenital rubella syndrome (CRS). CRS is a group of devastating birth defects that includes blindness, deafness, and heart defects. More than 100,000 children are born every year with CRS, mainly in Africa, South-East Asia, and the Western Pacific.1,2 Rubella vaccine is highly effective and safe when used across a population and, as a result, endemic rubella transmission has been interrupted in the Americas since 2009. Incomplete rubella vaccination programs result in continued disease transmission as evidenced by large outbreaks in recent years in Japan and elsewhere. Countries with high rates of susceptibility to rubella among women of childbearing age are at highest risk for CRS. This risk varies between and within countries based on epidemiological and socioeconomic differences.3 Economic burden studied in Romania suggests high cost and considerable impact of Rubella outbreaks4. While much progress has occurred, rubella remains an important pathogen of public health concern around the world. For example, the rubella epidemic in Japan, with more than 11,000 rubella cases occurring in the first 6 months of 2013 and at least 13 CRS cases occurring, highlights the fact that a partial vaccination strategy leads to major outbreaks. Seventy percent of the rubella cases in the Japanese outbreak occurred among males ages 20 to 39 years, indicating the weakness of an initial strategy that provided rubella vaccine only to adolescent girls, common in some countries. In 2012, Poland and Romania also experienced rubella outbreaks that predominantly affected males as a result of a vaccination strategy that initially focused on vaccination of females. For this reason, a global commitment to rubella control, elimination, and eventual eradication must be in place. Rubella virus is a candidate for global eradication because humans are the only known host, safe and highly effective vaccines (more than 95% following a single dose) exist, accurate diagnostic and molecular assays exist and are key to guiding the eradication of Rubella, and there has been demonstration of sustained interruption of endemic transmission in the Americas since 2009. Data from different African countries suggests that rubella virus is common. References: 1. http://www.emro.who.int/health-topics/rubella/disease-and-epidemiology.html 2. https://www.cdc.gov/globalhealth/measles/facts.htm 3. Nathaniel Lambert, Peter Strebel, Walter Orenstein, Joseph Icenogle, and Gregory A. Poland. Rubella. Author manuscript; PMC 2016 Jun 6. Lancet. 2015 Jun 6; 385(9984): 2297–2307. Published online 2015 Jan 8.doi: 10.1016/S0140-6736(14)60539-0 4. Njau J, Janta D, Stanescu A, et al. Assessment of Economic Burden of Concurrent Measles and Rubella Outbreaks, Romania, 2011–2012. Emerging Infectious Diseases. 2019;25(6):1101-1109. doi:10.3201/eid2506.180339. Review: Elise Bouthry, Olivier Picone Ghada Hamdi, Liliane Grangeot-Keros, Jean-Marc Ayoubi and Christelle Vauloup-Fellous. Rubella and pregnancy: diagnosis, management and outcomes 2014 Prenatal Diagnosis DOI: 10.1002/pd.4467 Review: J.M. Hübschen, S.M. Bork, K.E. Brown, A. Mankertz, S. Santibanez, M. Ben Mamou, M.N. Mulders, C.P. Muller. Challenges of measles and rubella laboratory diagnostic in the era of elimination. August 2017 Volume 23, Issue 8, Pages 511–515. DOI: https://doi.org/10.1016/j.cmi.2017.04.009

8. Potential public health impact of the test:

Please explain in which way the proposed test benefits public health. Please detail your response and add references:
Given the high incidence of Rubella, noted above, and the fact that several countries have not gained elimination as an intended goal, laboratory investigation by IgG testing is essential to attaining this goal, posing a huge positive public health impact. The presence of IgG antibodies to rubella virus indicates a previous exposure either by vaccination or prior rubella infection and suggests immunity.3 Seroconversion of specific rubella antibodies or a significant rise of the IgG titer strongly supports the diagnosis of acute rubella infection.3 The quantitative determination therefore, of specific IgG is used to determine the immune status to rubella and distinguish between those who have been exposed in the past and those who may have active infection.3 The use of IgG testing can help with identification of natural immunity or immunity gained by vaccination thus it may not be necessary to vaccinate entire populations where records are not as well kept by using the diagnostic. In eradication efforts, this test is crucial to detecting patients needing the vaccine. In countries where the virus has been rampant, natural immunity can be established to reserve the vaccine for the most vulnerable patients such as women who intend to become pregnant, but also for the general population for attaining eradication. References: J.M. Hübschen, M. Bork, E.Brown, A.Mankertz, S.Santibanez, M.BenMamou, M.N.Mulders, C.P. Muller1 Challenges of measles and rubella laboratory diagnostic in the era of elimination. Clinical Microbiology and Infection. Volume 23, Issue 8, August 2017, Pages 511-515 Mirambo, M. M., Majigo, M., Aboud, S., Groß, U., & Mshana, S. E. (2015). Serological makers of rubella infection in Africa in the pre vaccination era: a systematic review. BMC research notes, 8, 716. doi:10.1186/s13104-015-1711-x https://diagnostics.roche.com/global/en/products/params/elecsys-rubella-igg.html

9. Clinical utility of the proposed test/potential impact of the test on patient management and care

Please provide your answer as described in the guidance document:
Peri-natal testing: Given that Rubella is common in Africa, there are a significant number of susceptible women of childbearing age which means that the potential risk of giving birth to a child with CRS is relatively high. Diagnostic screening tests will provide a high impact on intervention with vaccines and patient outcomes. Surveillance: A French survey found that the proportion of people 18–32 years old susceptible to both measles and rubella infections remained high in France even after the promotion campaigns about vaccination catch-up during and following the major measles epidemic in 2009–2011, further suggesting the importance of diagnostic intervention for follow-up. An Australian serological test survey prior to and after a vaccination campaign found that susceptibility to rubella varied considerably between age groups and by sex. Before a vaccination campaign 40% of children aged 10–12 years were susceptible to rubella. They were too old to have received rubella vaccine in infancy and too young to have received an adolescent dose. These differences disappeared after the campaign and only 6% of preschool and 5% of primary school aged children remained susceptible, again suggesting the importance of Rubella IgG assessment. References: Lambert, N., Strebel, P., Orenstein, W., Icenogle, J., & Poland, G. A. (2015). Rubella. Lancet (London, England), 385(9984), 2297–2307. doi:10.1016/S0140-6736(14)60539-0 Mirambo, M. M., Majigo, M., Aboud, S., Groß, U., & Mshana, S. E. (2015). Serological makers of rubella infection in Africa in the pre vaccination era: a systematic review. BMC research notes, 8, 716. doi:10.1186/s13104-015-1711 Antona, D., Morel, P., Jacquot, C., Fonteneau, L., Dina, J., Vauloup-Fellous, C., … Lévy-Bruhl, D. (2019). Measles and rubella seroprevalence in a population of young adult blood donors, France 2013. Epidemiology and infection, 147, e109. doi:10.1017/S0950268819000050 Gilbert, G. L., Escott, R. G., Gidding, H. F., Turnbull, F. M., Heath, T. C., McIntyre, P. B., & Burgess, M. A. (2001). Impact of the Australian Measles Control Campaign on immunity to measles and rubella. Epidemiology and infection, 127(2), 297–303. doi:10.1017/s0950268801005830

10. Systematic reviews of the clinical accuracy of the test

Please describe or comment as requested in guidance document or state if no systematic review of clinical accuracy studies exists:
None available

Please attach the reviews you make reference to:

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11. Primary studies of clinical accuracy of the test

Please describe or comment as requested in the guidance document or state if no primary studies of clinical accuracy are available:
CLINICAL ACCURACY OF IgG TESTS IN PRE-PREGNANCY AND PERI-NATAL SCREENING Enders, M., Bartelt, U., Knotek, F., Bunn, K., Strobel, S., Dietz, K., & Enders, G. (2013). Performance of the Elecsys Rubella IgG assay in the diagnostic laboratory setting for assessment of immune status. Clinical and vaccine immunology : CVI, 20(3), 420–426. doi:10.1128/CVI.00688-12 ABSTRACT Rubella in early pregnancy bears a high risk for congenital defects (e.g., cataracts, hearing loss, and heart disease) and for long-term sequelae in the newborn. Despite implementation of vaccination programs in many regions, the threat of devastating consequences from congenital rubella virus infection remains. Careful screening of maternal immune status before and during pregnancy helps to reduce the risk. This study compared the performance of the Elecsys Rubella IgG assay with that of other assays routinely used for screening. Samples from 1,090 women undergoing routine antenatal care were tested using the Elecsys and Enzygnost Rubella IgG assays and the hemagglutination inhibition test. Samples with hemagglutination inhibition titers of less than 32 (n = 148) were additionally tested using the Vidas, AxSYM, Liaison, and Architect Rubella IgG assays. Agreement of qualitative results from the Elecsys, Enzygnost, and hemagglutination inhibition assays was good in all samples. All assays showed 100.0% specificity. In samples with hemagglutination inhibition titers of less than 32, the Elecsys, AxSYM, and Enzygnost assays showed higher sensitivity (more than 90.0%) than the other immunoassays (78.6 to 82.4%). The Elecsys assay reported significantly higher rubella virus IgG levels than the other immunoassays across the whole set of 1,090 samples, with the largest bias and deviation from limits of agreement in Bland-Altman analysis. In conclusion, the Elecsys assay is highly sensitive and specific with regard to qualitative results and suitable for routine automated screening. However, given the considerable variation between quantitative results from different immunoassays, testing methods should be documented and the same assay used throughout an individual's antenatal follow-up wherever possible. CLINICAL ACCURACY OF IgG TESTS IN ROUTINE SCREENING AND DIAGNOSIS OF ACUTE INFECTION: The following article discusses the clinical accuracy of diagnostic assays on Rubella patients and includes routine screening and patients with acute infection: Dimech, W., Panagiotopoulos, L., Francis, B., Laven, N., Marler, J., Dickeson, D., … Dax, E. M. (2008). Evaluation of eight anti-rubella virus immunoglobulin g immunoassays that report results in international units per milliliter. Journal of clinical microbiology, 46(6), 1955–1960. doi:10.1128/JCM.00231-08 An evaluation of anti-rubella virus immunoglobulin G (IgG) immunoassays that report in international units per milliliter (IU/ml) was performed to determine their analytical performance and the degree of correlation of the test results. A total of 321 samples were characterized based on results from a hemagglutination inhibition assay. The 48 negative and 273 positive samples were used to determine the sensitivity and specificity of the assays. When equivocal results were interpreted as reactive, the sensitivity of the immunoassays ranged from 98.9 to 99.9% and the specificity ranged from 77.1 to 95.8%. All assays had positive and negative delta values of less than 2. A significant difference between the mean results of all assays was demonstrated by analysis of variance. However, post hoc analysis showed there was good correlation in the mean results expressed in IU/ml between some of the assays. Our results show the level of standardization between anti-rubella virus IgG immunoassays reporting results expressed as IU/ml has improved since a previous study in 1992, but further improvement is required.

Please attach the publications you make reference to:

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12. Systematic reviews of the clinical utility/impact of the test on patient management and care

Please describe any systematic reviews of studies on the impact of the test result in clinical practice on diagnosis, treatment and patient outcomes or state if none are available (please refer to the guidance document)

SYSTEMATIC REVIEWS FOUND ALL FOCUS ON PERI-NATAL STUDIES:

Isabelle Boucoiran, Eliana Castillo, Rubella in Pregnancy; J. Obstetrics and Gynaecology, Canada. No 368, December 2018 https://www.jogc.com/article/S1701-2163(18)30569-3/pdf

ABSTRACT

Objective
To review the epidemiology, natural history, evaluation, and prevention of rubella infection during pregnancy. This will aid obstetric care providers in counseling their patients regarding potentially devastating effects on the developing fetus and the importance of vaccinating susceptible women as appropriate.

Outcomes:
Outcomes evaluated include fetal rubella infection, maternal seroconversion and response to rubella-containing vaccines.

Evidence:
Medline, PubMed, EMBASE, and Cochrane databases were searched for articles in English on subjects related to rubella infection during pregnancy between 1985 and 2017. Results were restricted to systematic reviews, randomized controlled trials/controlled clinical trials, and observational studies. Other (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Valuation methods:
The quality of the evidence is rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1). Recommendations for practice are ranked according to the method described in this Report.

Guideline update
The guideline will be reviewed 5 years after publication to decide if an update is required. However, if important new evidence is published prior to the 5-year cycle, the review process may be accelerated for a more rapid update of some recommendations

Sponsor: Society of Obstetricians and Gynaecologists of Canada.

Recommendations:
1. Screening for rubella serostatus is recommended as part of standard prenatal screening if a pregnant woman has no record of rubella past immunity and no proof of immunization against rubella (III-B).
2. Since the effects of rubella infection in pregnancy vary with the gestational age at the time of infection, accurate gestational dating should be established, as well as timing of rubella infection, as they are critical to counselling (II-3A).
3. In a pregnant woman exposed to rubella or who develops signs or symptoms of rubella or whose fetus presents ultrasound anomalies compatible with congenital rubella syndrome, serological testing for rubella immunoglobulin M and immunoglobulin G should be performed to determine immune status and risk of congenital rubella syndrome (III-A).
4. Women should be counselled about the possible risk of vertical transmission and informed regarding the option of pregnancy termination, especially if primary infection occurs prior to 16 weeks gestation (III-A).
5. Rubella immunization should not be administered in pregnancy but may be safely given postpartum, as long as there is no contraindication to receive a live vaccine (i.e., systemic immunosuppression). Consider delaying vaccination if the woman received any immunoglobulin-containing preparations, including Rh immunoglobulin or intravenous immune globulin, or blood products during pregnancy or the peripartum period, as there is potential for reduced vaccine effectiveness (III-B).
6. Women who have been inadvertently vaccinated in early pregnancy or who become pregnant immediately following vaccination can be reassured that there have been no cases of congenital rubella syndrome documented in these situations (III-B).
7. Women wishing to conceive should be counselled and encouraged to have their rubella antibody status determined if no record of rubella past immunity and no proof of immunization are available and undergo rubella vaccination if needed (III-B).

Systematic Reviews on utility of Rubella Screening and infection are sparse but the following review highlights the gaps and need for more serological data to be able to eradicate Rubella. This supports the importance of the use of diagnostic assays for future eradication of the disease.

Kimberly M. Thompson1,2,∗ and Cassie L. Odahowski1. Systematic Review of Measles and Rubella Serology Studies Risk Analysis, Vol. 36, No. 7, 2016 DOI: 10.1111/risa.12430

Abstract:
Serological tests provide information about individual immunity from historical infection or immunization. Cross-sectional serological studies provide data about the age-and sex-specific immunity levels for individuals in the studied population, and these

data can provide a point of comparison for the results of transmission models. In the context of developing an integrated model for measles and rubella transmission, we reviewed the existing measles and rubella literature to identify the results of national serological studies that provided cross sectional estimates of population immunity at the time of data collection. We systematically searched PubMed, the Science Citation Index, and references we identified from relevant articles published in English. We extracted serological data for comparison to transmission model outputs. For rubella, serological studies of women of child-bearing age provide information about the potential risks of infants born with congenital rubella syndrome. Serological studies also document the loss of maternal antibodies, which occurs at different rates for the different viruses and according to the nature of the induced immunity (i.e., infection or vaccine). The serological evidence remains limited for some areas, with studies from developed countries representing a disproportionate part of the evidence. The collection and review of serological evidence can help program managers identify immunity gaps in the population, which may help them better understand the characteristics of individuals within their populations who may participate in transmission and manage risks.

The following information was obtained from a seroprevalence study taken from the following Systematic Review paper:

Anna Lena Lopez, Peter Francis N. Raguindin, Maria Asuncion Silvestre, Xenia Cathrine J. Fabay, Ariel B. Vinarao, and Ricardo Manalastas, “Rubella and Congenital Rubella Syndrome in the Philippines: A Systematic

Review,” International Journal of Pediatrics, vol. 2016, Article ID 8158712, 8 pages, 2016. https://doi.org/10.1155/2016/8158712.

2.2. Seroprevalence Survey

To determine the proportion of women who were susceptible, that is, seronegative for rubella, a cross-sectional study of pregnant women who consulted in the obstetric outpatient clinic of the Philippine General Hospital (PGH) in the city of Manila for antenatal care was conducted in 2001-2002. Sample size was computed based on the seroprevalence study of Alday [14] that 27% were seronegative in the urban population, and using an interval of 5 with a 95% confidence level, and a 25% dropout rate, then a minimum of 373 pregnant women were required. After obtaining informed consent, data collection forms were completed specifically noting the following: age, occupation, educational attainment, age of gestation, number of previous gestations, and history of rubella immunization. Blood was obtained from the subjects and stored at −20°C until ELISA for rubella was performed. Rubella-specific IgG was tested using commercially available enzyme-linked immunosorbent assay kit (CAPTIA™; Trinity Biotech, Clark Laboratories, TX, USA). ELISA was performed following the manufacturer’s instructions.

Data was entered in Microsoft Excel and analysed using Stata 7™ (Stata Corporation, TX, USA). Descriptive statistics for maternal data (age, educational attainment, number of previous gestations, age of gestation, occupation, and history of rubella immunization) and 95% confidence intervals (CI) were calculated. Tests for association of above factors with rubella susceptibility were determined using chi-square test or Fisher’s exact test when data were sparse, and statistical significance was set at p

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13. Primary studies of the clinical utility/impact of the test on patient management and care

Please briefly describe any primary studies of the clinical utility/impact of the test on patient management and care, or state if none are available (please refer to the guidance document):
RUBELLA SURVEILLANCE: The following paper demonstrates an example of the impact a campaign against Rubella using testing and vaccination can have. I think this study shows a great correlation between diagnostics and the ability to eradicate. Gilbert, G. L., Escott, R. G., Gidding, H. F., Turnbull, F. M., Heath, T. C., McIntyre, P. B., & Burgess, M. A. (2001). Impact of the Australian Measles Control Campaign on immunity to measles and rubella. Epidemiology and infection, 127(2), 297–303. doi:10.1017/s0950268801005830 To evaluate the impact of the 1998 Australian Measles Control Campaign on immunity to measles and rubella, 4400 opportunistically-collected sera, submitted to diagnostic laboratories across Australia from subjects aged 1–49 years, and 3000 from subjects aged 1–18 years, were tested before and after the campaign, respectively. Rubella immunity in 1–18 year-olds rose from 83% to 91% (P!0±001), again with significant increases in preschool (4%, P¯0±002) and primary school (16%, P!0±001) children. 94% of individuals aged 19–49 years were immune to rubella. These sero surveys confirm other evidence of the effectiveness of the Australian Measles/Rubella Control Campaign and demonstrate the value of sero surveillance using opportunistically collected sera. Before the campaign 40% of children aged 10–12 years were susceptible to rubella. They were too old to have received rubella vaccine in infancy and too young to have received an adolescent dose. These differences disappeared after the campaign and only 6% of preschool and 5% of primary school aged children remained susceptible. The following article shows clinical utility of the test for surveillance in a Japanese population: Kanamori H1, Tokuda K, Ikeda S, Endo S, Ishizawa C, Hirai Y, Takahashi M, Aoyagi T, Hatta M, Gu Y, Yano H, Weber DJ, Kaku M. Prevaccination antibody screening and immunization program for healthcare personnel against measles, mumps, rubella, and varicella in a Japanese tertiary care hospital. Tohoku J Exp Med. 2014 Oct;234(2):111-6 Abstract: Susceptible healthcare personnel (HCP) are at high risk for acquiring and transmitting measles, mumps, rubella, and varicella (MMRV). Presumptive evidence of immunity to MMRV is recommended for HCP. The aim of this investigation was to examine the seroprevalence of MMRV in Japanese HCP and the association with history or vaccination in terms of occupational safety. To improve infection control at our hospital, we also assessed their immune status by implementing prevaccination antibody screening and an immunization program with postvaccination serological testing. We implemented seroprevalence surveys on MMRV antibodies among 243 newly and 2,664 previously hired HCP in a Japanese tertiary care hospital. Self-administered questionnaires about history of MMRV and vaccination with or without written documentation were completed for newly hired HCP. Prevaccination and postvaccination serological tests were performed using virus-specific IgG enzyme-linked immunosorbent assays. Indeed, only a few HCP accurately remembered or had written records of their disease or vaccination history. After our immunization program was implemented, the seropositivity rate reached levels as high as ~98% for measles, rubella, and varicella, and increased to ~80% for mumps. Our program was cost-effective, and no severe adverse reactions were reported. The prevaccination antibody screening for HCP would be helpful, given the lack of written vaccination records or documented disease history, and is also useful for the prevention of adverse reactions associated with unnecessary vaccination. It is important for infection control practitioners to comprehend the immune status of HCP against MMRV, and then provide an appropriate immunization program for susceptible HCP. No studies were found showing the utility of rubella IgG testing for diagnosis of acute infection.

Please include the articles/documents of key primary studies and all publications you make reference to:

filecount - Please include the articles/documents of key primary studies and all publications you make reference to:
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14. Details of any guideline recommendations concerning use of the test

Briefly describe the specific recommendation (indicate where it can be found in the guideline) and summarise the evidence upon which it is based (indicating where it can be found in the evidence summaries):
WHO recommends that all countries that have not yet introduced rubella vaccine should consider doing so using existing, well-established measles immunization programmes. To-date, four WHO regions have established goals to eliminate this preventable cause of birth defects. In 2015, the WHO Region of the Americas became the first in the world to be declared free of endemic transmission of rubella. The number of countries using rubella vaccines in their national programme continues to steadily increase. As of December 2018, 168 out of 194 countries had introduced rubella vaccines and global coverage was estimated at 69%. Reported rubella cases declined 97%, from 670 894 cases in 102 countries in 2000 to 14 621 cases in 151 countries in 2018. CRS rates are highest in the WHO African and South-East Asian regions where vaccination coverage is lowest. In April 2012, the Measles Initiative – now known as the Measles & Rubella Initiative – launched a Global Measles and Rubella Strategic Plan which covers the period 2012-2020. The Plan includes a series of global goals for 2020. By the end of 2020 •Achieve measles and rubella elimination in at least 5 WHO regions. Based on the 2018 Global Vaccine Action Plan (GVAP) Assessment Report by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization, rubella control is lagging, with 26 countries still to introduce the vaccine, while two regions (African and Eastern Mediterranean) have not yet set rubella elimination or control targets. SAGE recommends that rubella vaccination should be incorporated into immunization programmes, as quickly as possible, to ensure additional gains in controlling rubella can be made. As one of the founding members of the Measles & Rubella Initiative, WHO provides technical support to governments and communities to improve routine immunization programmes and hold targeted vaccination campaigns. In addition, the WHO Global Measles and Rubella Laboratory Network supports the diagnosis of rubella and CRS cases and tracking of the spread of rubella viruses. Enzyme immunoassays (EIA) are the most commonly used and widely available diagnostic test for rubella IgG and IgM antibodies and are sensitive and relatively easy to perform Detection of IgG antibody to screen for rubella immunity: A single serologic IgG test may be used to determine the rubella immune status of persons whose history of rubella disease or vaccination is unknown. The presence of serum IgG rubella-specific antibodies indicates immunity to rubella. https://www.who.int/news-room/fact-sheets/detail/rubella https://www.cdc.gov/vaccines/pubs/surv-manual/chpt14-rubella.pdf

Please attach the guidelines that you are refering to:

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15. Examples of commercially available IVD products in the proposed new category

Please download and complete the table in Annex I with commercially available IVD products in the test category, and include the information listed for each one. Please upload the completed file back and all the relevant test Instructions For Use (Package Inserts):
[]

filecount - Please download and complete the table in Annex I with commercially available IVD products in the test category, and include the information listed for each one. Please upload the completed file back and all the relevant test Instructions For Use (Package Inserts):
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16. Training requirements

Considering the tests mentioned in 15 above, what in general are the training requirements?:
One-day training (in person or videoconference)

17. Equipment required

Considering the tests mentioned in 15 above, please describe in general terms what, if any, equipment is required other than that provided with the test:
Refrigerators, freezers. Incubators, pipettors, centrifuges, possible safety hood, vortex, microfuge

18. Energy requirements

Considering the tests mentioned in 15 above, what, if any energy source is required for performance of the tests?:
Continuous electrical power

Considering the tests mentioned in 15 above, what, if any energy source is required for performance of the tests?: [Other]

19. Landscape reviews

Please list any landscape reviews describing the different test technologies and their use or state if none available:
The article below gives an overview of the technologies used in detecting IgG: Dimech, W., Grangeot-Keros, L., & Vauloup-Fellous, C. (2016). Standardization of Assays That Detect Anti-Rubella Virus IgG Antibodies. Clinical microbiology reviews, 29(1), 163–174. doi:10.1128/CMR.00045-15 RUBELLA VIRUS IgG TESTS The serological diagnosis of rubella virus infection and immunity began in the early 1960s after the isolation of rubella virus. Initially, viral neutralization testing (NT) was introduced but this method was cumbersome, varied in sensitivity, and generally obtained low titers. NT was able to detect antibodies to both E1 and E2, and reactivity in this assay is still regarded as the most reliable indicator of protective immunity. NT was replaced by the HAI test (38). This test relies on the principle that the hemagglutinin on the virus agglutinates erythrocytes of a number of animal species, including pigeons and trypsinized human group O cells. HAI detects both IgG and IgM and may be falsely negative if rubella virus-specific antibodies other than those against hemagglutinin are present, e.g., anti-C protein antibodies. Nonspecific inhibitors of HAI such as low-density beta lipoproteins need to be removed from the serum sample prior to testing; this is usually achieved through incubation with kaolin (39). However, there are many reports that highlight the variability of HAI testing within and between laboratories. The sources of variation include variability in the selection of reagents (i.e., different species and qualities of erythrocytes); potency of viral antigen; and methodologies, including temperature and time of incubation, pH of reagents, and different buffering systems; and interreader variability (40,–42). An alternative test system used in early rubella virus antibody testing was the complement fixation test (CFT), a test that relies on the detection of complement usage during an antibody-antigen reaction (38). Like HAI, CFT was labor intensive and imprecise and detected both IgG and IgM. Radial hemolysis (RH), which detects the ability of the antibody-antigen reaction to lyse erythrocytes immobilized in agar, was used to detect and semiquantify rubella virus antibodies (43,–47). In contrast to HAI and CFT, RH detects only IgG, in particular, subclasses 1 and 3. By testing a serial dilution of a standard in parallel with patient samples and constructing a standard curve based on the measurement of the annular radius of the zone of hemolysis created, IgG levels could be quantified. The early 1980s saw the introduction of EIA for the detection of specific antibodies (42, 48,–50). EIAs, which can be formatted to detect subclasses of antibodies or be directed toward specific antigens, quickly replaced HAI, CFT, and other assays to such an extent that today very few reference laboratories in the world still retain the capacity to perform these reference tests. Early commercial rubella virus IgG EIAs were usually in a microtiter plate format employing an enzymatic color-based detection system. The assays varied vastly in the choice of conjugate, substrate, and antigen, as well as incubation times and temperatures (51, 52). These assays usually demonstrated good linearity and had equivalent sensitivities and specificities. Many authors have compared the performance of EIAs over the years (52,–58). One of the first automated benchtop analyzers developed for the detection of rubella virus IgG was the Abbott IMx (59). Since then, microtiter plate technology has gradually been replaced by automated analyzers using a range of detection technologies such as immunofluorescence (bioMérieux VIDAS, Abbott AxSYM), electrochemiluminescence (Roche Elecsys), and chemiluminescence (Abbott Architect, DiaSorin Liaison, Siemens ADVIA Centaur). These changes have allowed rubella virus serology to be incorporated within general medical laboratory testing alongside general chemistry and endocrinology. Apart from the different technologies used in modern test systems, an array of different conjugates, substrates, and antigens are still used (54). A prime example is the Roche Elecsys rubella virus IgG assay, which uses several recombinant proteins as the antigen source, unlike most other assays, which use native rubella virus-derived antigens obtained as whole, purified, or partly purified virus or as a viral lysate. Irrespective of the format of the assay, all of the commercial rubella virus IgG assays currently available are calibrated against the same WHO international standard and report results quantitatively in international units per milliliter (54). Not all regulatory jurisdictions require rubella virus IgG assays to be calibrated solely by using the WHO international standard. In the United States, for example, the Code of Federal Regulations refers to a panel of 100 well-characterized rubella patient serum samples obtained from the Centers for Disease Control and Prevention to assess new assays (60).

Please attach the documents refered to in this question:
[{ "title":"Commercial rubella IgG assays","comment":"","size":"188.383","name":"Table%20WHO%20assays_IgG.pdf","filename":"fu_xujqs2ujts24y5j","ext":"pdf" }]

filecount - Please attach the documents refered to in this question:
1

20. Cost and Cost-effectiveness

Please provide a summary of data on comparative cost and cost-effectiveness or state if not available:

Cost effectiveness of the vaccine can translate to IVD value as treatment for CRS is very costly. CRS deals with peri-natal testing, the other categories are not found for cost analysis.

Babigumira, J. B., Morgan, I., & Levin, A. (2013). Health economics of rubella: a systematic review to assess the value of rubella vaccination. BMC public health, 13, 406. doi:10.1186/1471-2458-13-406

Abstract

Background
Peri-natal testing: Most cases of rubella and congenital rubella syndrome (CRS) occur in low- and middle-income countries. The World Health Organization (WHO) has recently recommended that countries accelerate the uptake of rubella vaccination and the GAVI Alliance is now supporting large scale measles-rubella vaccination campaigns. We performed a review of health economic evaluations of rubella and CRS to identify gaps in the evidence base and suggest possible areas of future research to support the planned global expansion of rubella vaccination and efforts towards potential rubella elimination and eradication.

Methods
We performed a systematic search of on-line databases and identified articles published between 1970 and 2012 on costs of rubella and CRS treatment and the costs, cost-effectiveness or cost-benefit of rubella vaccination. We reviewed the studies and categorized them by the income level of the countries in which they were performed, study design, and research question answered. We analyzed their methodology, data sources, and other details. We used these data to identify gaps in the evidence and to suggest possible future areas of scientific study.

Results
We identified 27 studies: 11 cost analyses, 11 cost-benefit analyses, 4 cost-effectiveness analyses, and 1 cost-utility analysis. Of these, 20 studies were conducted in high-income countries, 5 in upper-middle income countries and two in lower-middle income countries. We did not find any studies conducted in low-income countries. CRS was estimated to cost (in 2012 US$) between $4,200 and $57,000 per case annually in middle-income countries and up to $140,000 over a lifetime in high-income countries. Rubella vaccination programs, including the vaccination of health workers, children, and women had favorable cost-effectiveness, cost-utility, or cost-benefit ratios in high- and middle-income countries.

Conclusions
Treatment of CRS is costly and rubella vaccination programs are highly cost-effective. However, in order for research to support the global expansion of rubella vaccination and the drive towards rubella elimination and eradication, additional studies are required in low-income countries, to tackle methodological limitations, and to determine the most cost-effective programmatic strategies for increased rubella vaccine coverage.

The following article does discuss cost effectiveness of antibody screening of Rubella in a Japanese population:

Kanamori H1, Tokuda K, Ikeda S, Endo S, Ishizawa C, Hirai Y, Takahashi M, Aoyagi T, Hatta M, Gu Y, Yano H, Weber DJ, Kaku M. Prevaccination antibody screening and immunization program for healthcare personnel against measles, mumps, rubella, and varicella in a Japanese tertiary care hospital. Tohoku J Exp Med. 2014 Oct;234(2):111-6

Abstract:
Susceptible healthcare personnel (HCP) are at high risk for acquiring and transmitting measles, mumps, rubella, and varicella (MMRV). Presumptive evidence of immunity to MMRV is recommended for HCP. The aim of this investigation was to examine the seroprevalence of MMRV in Japanese HCP and the association with history or vaccination in terms of occupational safety. To improve infection control at our hospital, we also assessed their immune status by implementing prevaccination antibody screening and an immunization program with postvaccination serological testing. We implemented seroprevalence surveys on MMRV antibodies among 243 newly and 2,664 previously hired HCP in a Japanese tertiary care hospital. Self-administered questionnaires about history of MMRV and vaccination with or without written documentation were completed for newly hired HCP. Prevaccination and postvaccination serological tests were performed using virus-specific IgG enzyme-linked immunosorbent assays. Indeed, only a few HCP accurately remembered or had written records of their disease or vaccination history. After our immunization program was implemented, the seropositivity rate reached levels as high as ~98% for measles, rubella, and varicella, and increased to ~80% for mumps. Our program was cost-effective, and no severe adverse reactions were reported. The prevaccination antibody screening for HCP would be helpful, given the lack of written vaccination records or documented disease history, and is also useful for the prevention of adverse reactions associated with unnecessary vaccination. It is important for infection control practitioners to comprehend the immune status of HCP against MMRV, and then provide an appropriate immunization program for susceptible HCP.

The following abstract looks relevant to cost in peri-natal screening but I was not able to find the full article:

A. K. LUGNÉR (a1), L. MOLLEMA (a1), W. L. M. S. J.M.HAHNÉ (a1) RUIJS (a2) (a3) A cost-utility analysis of antenatal

screening to prevent congenital rubella syndrome DOI: https://doi.org/10.1017/S0950268809991336 Published online by Cambridge University Press: 17 December 2009

In low vaccination coverage regions (LVR) in The Netherlands people often reject participation in the National Immunization Programme for religious reasons. During a rubella epidemic in 2004–2005, 32 pregnant women were notified with rubella, and 11 babies were born with defects related to maternal infection. This study presents a cost-utility analysis of a screening and vaccination programme for rubella focusing on three scenarios: (1) screening non-vaccinated pregnant women in LVR; (2) screening all pregnant women in LVR; (3) screening all non-vaccinated pregnant women in The Netherlands (including pregnant first-generation non-Western immigrant women). Cost-utility was estimated over a 16-year period which included two rubella outbreaks. Observed complications from the 2004–2005 epidemic were used to estimate average cost savings and quality-adjusted life-years (QALY) gained. The programme would be cost-effective (€1100/QALY gained) when assuming an acceptability of vaccination of 20% in women belonging to orthodox protestant risk groups.

21. Ethical issues

Please detail any important ethical considerations related to the proposed test category and any consequences of its use:
A debate exists regarding safety of the vaccine and related autism. There are groups that believe this is the case and thus creating a growing concern for the spread of the disease in countries where eradication is close to being achieved. Heller T. (2001). Ethical debate: Vaccination against mumps, measles, and rubella: is there a case for deepening the debate? How safe is MMR vaccine?. BMJ (Clinical research ed.), 323(7317), 838–840.

22. Equity and human rights issues

Please indicate if it reduces inequities and increases accessibility or if the test may prove inaccessible to some populations:
The use of Rubella IVD's to ensure eventual Rubella eradication is key to reducing inequity globally. The tests can identify individuals requiring the vaccine and support the need for more accessibility globally.

Signature

Through the electronic signature below, I acknowledge that I have provided appropriate information to support this submission. I acknowledge that WHO reserves the right to format and select the information provided as necessary and agree that the information will be publicly disclosed by WHO. [Electronic Signature (type your full name to sign):]
Mick Mulders

Through the electronic signature below, I acknowledge that I have provided appropriate information to support this submission. I acknowledge that WHO reserves the right to format and select the information provided as necessary and agree that the information will be publicly disclosed by WHO. [Date (yyyy-mm-dd):]
2019-12-21