Prevention of acquisition of cytomegalovirus infection in pregnancy through hygiene-based behavioral interventions: A systematic review and gap analysis

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Disclosure of interest

The authors declare that there are no conflicts of interests.

ABSTRACT

Background

Congenital cytomegalovirus (cCMV) infection is the most common non-genetic cause of sensorineural hearing loss in childhood and an important cause of neuro-disability. There is no licensed CMV vaccine and no antenatal treatment for congenital CMV that is routinely recommended in clinical practice in the UK.

Objectives

To review the published literature for studies that evaluated preventative hygiene-based interventions in pregnancy for their impact on knowledge about CMV prevention, the uptake of preventative behaviors or the acquisition of CMV in pregnancy.

Search Strategy

Searches were carried out in OVID Medline database and CINAHL.

Selection Criteria

All human studies, limited to women of childbearing age were included.

Data Collection and Analysis

Two reviewers independently assessed the quality of the methods and results of included articles. Extracted data were classified using Cochrane guidelines.

Main Results

Seven studies met the inclusion criteria. These show that preventative measures are acceptable to pregnant women, can impact their behavior, and have the potential to reduce CMV in pregnancy. They are limited by several factors; sample size, non-randomized trial design and interventions that are beyond routine clinical practice.

Conclusions

An effective intervention that changes behavior in pregnancy and reduces the risk of CMV acquisition is needed as part of routine care. There is currently insufficient evidence about the form that this intervention should take.

Registration

PROSPERO registration number: CRD42017069666

Introduction

Cytomegalovirus (CMV) is the most common congenital infection in the UK. The estimated birth prevalence of congenital CMV (cCMV) is 0.3 - 0.7% [1,2] and it is more common than many better known congenital conditions, such as Down's Syndrome, spina bifida or cystic fibrosis.[3- 6]

The clinical presentation of CMV is wide-ranging. Around 10-15% of infants with congenital CMV will be symptomatic at birth and of these 40-60% will have life-long adverse sequelae, such as sensorineural hearing loss (SNHL), physical or cognitive impairment.[2,3,7]Of those babies who have no clinical features of congenital CMV at birth, around 10-15% will develop long term sequelae, particularly SNHL.[2,7] CMV infection is the leading non-genetic cause of SNHL and the only potentially treatable condition.[2,8,9,10]

Congenital CMV represents a significant public health issue, but there are currently no licensed CMV vaccines and no treatment for antenatal CMV infection routinely offered in the UK[11] or worldwide.[12] CMV is transmitted through contact with infected bodily fluids and pregnant women most commonly acquire infection through exposure to the saliva and urine of young children, especially their own children.[13] Reduction of pregnant women's contact with infected urine or saliva from young children has therefore been identified as one of the most important potential preventative strategies to reduce antenatal CMV infection.[14,15,16] Such advice is not

routinely provided as part of routine antenatal care in the majority of settings worldwide; however, advice is available online if women seek it, for example from the Centre for Disease Control and Prevention,[17]CMV Action,[18] and the NHS.[19]

Pregnant women are a group who are highly motivated to change behavior to protect the health of their developing fetus and are more receptive to healthcare messages than non-pregnant women.[20] For example, a UK longitudinal study reported a notable reduction in smoking, alcohol consumption and intake of caffeinated drinks when women became pregnant, compared with the period before pregnancy.[21] Furthermore, hygiene-based interventions can prevent other infectious diseases with similar transmission modes.[22,23,24]

In the U.K., a recent qualitative study conducted on pregnant women suggested that that they felt let down by antenatal services as they were not told about CMV and therefore, did not have the opportunity to make decisions for themselves about whether to make changes to reduce their risk of CMV.[25]

In this systematic review we sought to evaluate the published literature for studies that evaluated preventative hygiene-based interventions in pregnancy for their impact on knowledge about CMV prevention, the uptake of preventative behaviors or the acquisition of CMV in pregnancy.

Methods

Study design

The protocol for this study was designed using the Preferred Reporting Items For Systematic Review and Meta-Analysis Protocols and included the objective of the search, the search strategy, eligibility criteria and planned methods of quality assessment. PROSPERO registration number: CRD42017069666.

Selection of studies

The literature search was conducted using Medline and CINAHL databases and the Clinical Trials Registry of the National Institutes of Health was also searched to identify ongoing studies. No time limit was set. The reference lists of relevant articles were also searched, and additional studies were included if they fulfilled the inclusion criteria. The following search terms were used in different combinations: congenital cytomegalovirus, antenatal, prenatal, prevention, hygiene, intervention, pregnancy, hand wash, infection control. The full search strategy can be found in supplementary information. The literature search was completed in February 2019.

We included all randomized controlled trials (RCTs), non-randomized controlled trials, observational studies and case series. Studies were required to have included some women who were pregnant, of child bearing age or attempting pregnancy; studies were only included if they were reported in English; studies that tested interventions to prevent CMV infection via other routes of transmission or in other groups of patients (i.e. HIV, transplant, blood transfusions) were excluded. There were no publication date restrictions. Outcome measures included: effectiveness of

hygiene-based interventions (e.g. on cCMV or on seroconversion rate), adherence to protective behaviors, barriers to behavior change, adverse effects of intervention and change in knowledge about CMV.

Title and abstract screening using the above inclusion and exclusion criteria, was performed by three blinded reviewers (VB, AC, CJ) using Rayyan QCRI. The full text versions were reviewed in a blinded manner by the same authors. Any disagreements were resolved through arbitration from the other authors (TV). In addition, manual searching of full texts' reference list was undertaken.

Data extraction and management

Data was extracted independently by two authors (AC and VB) using a standardized extraction form.[26] Data extracted included: location, study design, sample, intervention, randomization procedure, blinding, nature of control group, method of outcome assessment and results.

Risk of bias assessment

Two authors (VB and AC) independently reviewed the studies that met the inclusion criteria and assigned a quality rating determined by the number of valid criteria met. An overall validity assessment rating for each trial was applied using the Cochrane Risk of Bias tool.[25] If there was any disagreement after unblinding, a third author arbitrated (TV).

Methodologic strength of RCT's was evaluated using the following criteria: allocation concealment, blinding of outcome assessors and completeness of follow up data and

for non-experimental studies: control of confounding variables, blinding of outcome assessors and completeness of follow-up data. If one or more validity criteria were not met, the study was considered to have a high risk of bias.

Data synthesis

Individual study characteristics were summarized in a descriptive table.

Results

The search yielded 763 articles, 447 of which were selected for abstract evaluation, 13 for full text evaluation and 7 for inclusion in the systematic review. Reason for exclusion can be found in Figure 1. Characteristics and scores of methodologic quality of the seven studies can be found in Table 1.

[Figure 1 here]

[Table 1 here]

The significant heterogeneity among the included studies prevented us from conducting a meta-analysis in order to pool their results.

Three studies were randomized controlled trials,[20,27,28] two were pre-test post-test design,[29,30]one was a case series[31] and one was an observational study.[32] The studies were conducted in the USA,[20, 27-30] France[31] and Italy.[32]

The study populations were varied. Three exclusively recruited pregnant women,[28,31,32] two recruited women with a young child who were either pregnant or

planning a pregnancy,[20,30]one recruited women with a young child in day care irrespective of their pregnancy status[27] and one recruited exclusively non-pregnant women with a young child in day care.[29]

Intervention

In Adler et al. (1996)[27] 50 mothers were randomized to one of three groups. Mothers in the education intervention (E) were given written and oral instructions for protective behaviors (frequent hand washing, wearing gloves for diaper changing and avoiding intimate contact with their child) and bi-weekly home visits were conducted to assess adherence *(n=11).* A second education intervention group (A) included an additional demonstration and practice of hand washing and glove changing techniques, as well as bi-weekly home visits with a research nurse to problem solve and provide positive reinforcement *(n=8).* The control group (C) received basic information about CMV but no intervention *(n=17)* and the fourth group of pregnant women (P) received an intervention equivalent to the education group (E), with the exception of home visits *(n=14).*

Building on the initial study, the same authors conducted a second study[20], where mothers *(n=115)* in the intervention group received the identical intervention as mothers in the initial study[27] who were randomized to the adherence and education group (A) with the addition of an educational video demonstrating protective techniques for avoiding acquisition of CMV (length of video unknown). The control group (C) received basic information about CMV but no intervention (*n=51*). The other difference in this trial was that mothers in the intervention group were informed of their serological status but were unaware if their child was shedding CMV.

In the only case series study,[31] pregnant women *(n=5312)* were provided with hygiene counselling on CMV prevention. Detailed oral and written hygiene information was given to seronegative mothers (and partners) by an obstetrician or midwife at the first general visit (12 WG). The information given was similar to 1996 Adler et al.[27] study, except wearing protective gloves was not recommended.

The intervention in the Revello et al.[32] study included pregnant women *(n= 646)* undergoing genetic screening in a hospital who have frequent contact with young children (own child or working with children < 36 months) and who were either CMV-seronegative or had not tested for CMV immune status. Seronegative women in the intervention group *(n=331)* received a 15-minute written information session explaining potential techniques for avoiding CMV acquisition and were given pictorial cards showing protective and risky behaviors to take home. In addition, a 5-minute session at follow-up visits (18 WG) and a questionnaire every 6 weeks from 18 weeks of gestation was scheduled to reinforce hygiene messages.

In Hughes et al.[28] pregnant women *(n=223)* who were screened for CMV serology during prenatal care before 20 WG were randomized into either the intervention group *(n= 124)* or the standard care group *(n= 63)* based on their serostatus (positive or negative). The intervention consisted of a 5-minute in office video with hygiene teaching, a take home calendar and weekly text message reminders. The control group received standard care in the form of a brochure about CMV acquisition. Those with primary CMV infection were excluded.

In the earliest reported study,[29] the intervention was administered to non-pregnant mothers *(n=11)* of young children (< 18 months of age). The intervention consisted of a 15-minute education session for each mother with a physician and written instructions about protective and risky behaviors similar to the previous studies. In addition, mothers were provided with gloves and soap at weekly home visits. Adherence was measured by self-reported percentages (0–100%) of protective or risky behaviors conducted each week for 6 weeks. The number of gloves, and soap remaining at each weekly home visit also measured adherence to protective behaviors.

Lastly, in the study by Price at al.[30] women who were pregnant *(n=328)* or planning a pregnancy and who had a child under the age of 5 *(n=481)* were randomly assigned to one of two intervention groups to test the effect of two educational based interventions to determine whether they increase knowledge about CMV, motivate information seeking behavior and lead to adoption of CMV prevention behaviors. In the first intervention women *(n=404)* were shown a one-page fact sheet about CMV acquisition and prevention strategies. In the second intervention women *(n=405)* were shown a 5-minute video, which included a first-person story of mothers' experiences with CMV, and information on acquisition of CMV and preventative strategies by a physician.

Change in knowledge

Only one paper explicitly investigated change in knowledge following an educational intervention.[30] Twelve questions assessed CMV knowledge before and immediately after presentation of CMV health education material. Questions were in 'true' or 'false' format and related to transmission of CMV. In this study the knowledge score

increased significantly after presentation of the film or factsheet ($P = < 0.001$) with a suggestion that the video may have been more effective than the factsheet.

Change in behavior

Six of the papers assessed participants' attitudes and behaviors to CMV prevention, although the methods varied.[20, 27-30,32]Three studies exclusively used self-reporting for assessment of the change in attitudes to preventative behaviors following the educational intervention.[27,30,32] Price et al.[30] used a survey delivered before and after one of the two interventions where participants recorded their level of agreement with a series of statements about engagement with preventative behaviors. They found that participants were strongly in agreement with the statements after receiving both of the educational materials (film or written information). In Revello et al.[32] participants were asked about actual behaviors by completing a questionnaire every 6 weeks from 18 weeks and found that the respondents followed the recommendations often (66%) or always (14%). Hughes et al.[28] also asked about current compliance with hygiene precautions at baseline and after the intervention or comparison. They found that reported behavioral compliance increased more in the intervention group than the control group ($P = 0.007$), although the qualitative data suggested that both the intervention group (behavioral intervention in clinic) and the control group (written information only) changed their behaviors.

Three papers included an objective assessment alongside self-reported measures of behavior change.[20,27, 29] In all three, women were asked about the percentage of opportunities where they performed protective or risky behaviors and measured soap and glove use. In Finney et al.[29] they reported an increase in protective behaviors and

a decrease in risky behaviors following education which was supported by the objective assessment. Adler et al's.[27] first study reported more self-reported hand washing in the group who received the enhanced intervention compared with the standard educational intervention but with no difference in the objective assessment of soap use, and in the later study,[20] no association between self-reported behavior change and objective assessment of adherence was reported.

Reduction of acquisition of CMV

Four studies assessed the impact of an intervention on rates of seroconversion,[20, 27,31,32] with two reporting that educational interventions significantly reduced seroconversion in participants.[31,32] Firstly, Revello et al.[32] showed a significantly lower seroconversion rate in the intervention (4/331) compared with the comparison (24/315) group (P = <0.001), which remained significant after adjustment for potential cofounders. This reduction rate equates to a number needed to treat of 16 (95% CI: 10-30). The second study[31]showed reduced seroconversion in the period following the educational intervention provided at around 12 WG (5/2583), compared with the first 12 weeks of pregnancy (11/2594), giving a significantly lower infection rate per woman in the period between 12 and 36 WG (0.008%) than in the period before 12 weeks (0.035%). Among the 16 women who seroconverted, 15 were at high risk of infection, 12 women had a child younger than the age of 3 at home, and 7 were paediatric nurses or doctors. This supports the need for hygiene information to be focused on the handling of young children. The lower incidence of CMV infection after 12 WG is also an important result as the risk for more serious damage to the fetus occurs with early trimester infection.[33] Therefore, the timing of any intervention must be considered.

In Adler et al's[27] first study they reported non-significantly reduced rates of seroconversion between intervention (E: 4/11, A: 2/8, P: 0/14) and control groups (8/17, $P < 0.29$). This study also showed that the rate of infection was statistically lower in pregnant women compared to non-pregnant women irrespective of the randomized group. In Adler et al.'s[20] subsequent study they reported no difference in the seroconversion rate between the intervention and control groups (9/115 in both groups) but reported significantly reduced seroconversion in those pregnant (1/17) at the time of enrolment compared with women attempting conception (10/24, $P = 0.008$). These results suggest that an intervention for pregnant women is effective because these women will perceive a higher risk and be more motivated to adhere to recommendations than non-pregnant women.

Acceptability

Three papers assessed acceptability of educational interventions for CMV risk reduction in pregnancy. Overall, it was found that interventions were not associated with adverse effects such as alarm, early termination of pregnancy[31] or an increase in psychological distress[28] and that recommendations were perceived to be worth providing to all pregnant women at risk of infection.[32]

Discussion

Main Findings

The findings from this review provide preliminary support for the implementation of hygiene-based interventions in pregnancy, but the studies are heterogeneous in their study populations, the interventions being offered and the outcomes being studied, which makes it hard to draw firm conclusions about the comparative value of the interventions being offered.

The one study which commented on change in knowledge reported an increase following the educational intervention[30] and all of the studies which reported on changes in preventative behaviors or attitudes towards them showed that the educational intervention did change attitudes, behaviors or predicted behaviors in women if they were pregnant, but the differences in the studies make it hard to fully understand the impact of separate educational interventions. Two of the four papers which investigated rates of seroconversion showed that hygiene-based interventions reduced the risk of seroconversion and both of these studies included only pregnant women.[31,32] The two papers which showed no statistically significant difference in rates of seroconversion included both pregnant and non-pregnant women and both of these commented that the rate of seroconversion was lower in pregnant women (although not significantly).[20,27] This may be because of behavioral differences in pregnancy or, as the authors suggest, that women in pregnancy are more motivated to engage with educational interventions and to make lifestyle changes.

Few papers investigated differences between different educational interventions but one study[30] suggested that the video may have been slightly more effective than the

factsheet, but that the difference was too small to be able to draw definitive conclusions. The broader health literature provides some support that interventions in video formats can be more effective than written,[34] particularly among low literacy populations.[35]

Strengths and Limitations

The studies in this review were of small sample size,[20,27] under-powered[27] or non-randomized [31,32] and the majority where carried out in the USA[20,27-29,31] and two countries within Europe,[31,32] limiting the extrapolation of results to healthcare settings in other countries. The diversity of the included populations, particularly the inclusion of both pregnant and non-pregnant participants, and the variation in healthcare settings and interventions make it hard to compare the impact of different interventions.

In the studies that assessed behavior change, [28, 30,32] self-report and indirect objective measures were used which may be unrelated to actual behavior change and so provides evidence about intended behavior change rather than actual behavior change. Therefore, this should be seen more as a marker of changes in attitude rather than behavior. Furthermore, one of the studies asked participants to reflect on whether their behavior would be different if they were pregnant, which is likely to yield different results than asking people about their current behavior.

In the Price et al study,[30] the post intervention assessments were conducted immediately after the intervention and it is therefore possible that if re-tested at a later time point, the impact might have been diminished. Importantly, there were no direct

behavioral measures (only self-reported data) in this study therefore it is not clear whether the women would actually adhere to these prevention behaviors.

The intensity of all of the interventions in this review and the consequent demands on staff are likely to be unrealistic in routine healthcare, all lasting between 10-20 minutes and requiring a medical professional. The interventions mostly took place during routine antenatal care visits and at one time point, which again is not feasible in routine healthcare as there is already so much to discuss in these visits. The current literature on alcohol prevention among pregnant women seems to point to the effectiveness of an intervention administered by a physician and integrated into obstetric care in primary care setting.[36-38]Although, interventions administered in a community setting and by non-professionals have also been found to reduce alcohol use among pregnant women.[39]

Three of the studies included instructions for glove use when diaper changing (in addition to washing hands) as a protective behavior,[20,27,29] which is unrealistic, impractical and is not included in the recommendations that can be found online.[17-19]

The replication of reinforcement methods that some of the studies use in this review such as home visits,[20,27] text message reminders[28] and frequent questionnaires [32] are also unrealistic in a routine clinical care setting. Therefore, it is clear that an intervention is needed which works not only in a clinical trial, but is feasible for routine healthcare.

Interpretation

The results suggest that, particularly in pregnancy, educational interventions may increase knowledge about CMV and how to prevent it, increase compliance with preventative behaviors and reduce seroconversion, but the heterogeneous nature of the current studies make it hard to generate firm conclusions.

In addition, the results also suggest that pregnant women are highly motivated to change their behavior in order to protect their fetus. This supports a wider literature that suggests pregnant women (and those attempting conception) are highly motivated to adopt positive lifestyle changes,[21,36-38] making this group of women more receptive to healthcare messages.

Conclusion

An effective intervention is needed that can reduce the risk of CMV acquisition in pregnancy and can be offered as part of routine healthcare. There is insufficient evidence at present about the form that this intervention should take as the studies to date are based on intensive counselling requiring more time from healthcare professionals than would typically be available within routine maternity care. Large scale RCTs are needed to assess the effectiveness of an educational intervention on antenatal acquisition of primary CMV infection and determine the feasibility of this approach in a routine healthcare context.

Disclosure of interest

The authors declare that there are no conflicts of interests.

Contribution to authorship

Study protocol was written by CJ, TV, AC, VB. All other authors reviewed the protocol. VB and AC performed the literature search, data extraction and analysis; CJ and TV were consulted in situations where AC and VB disagreed. All other authors contributed equally in supervising the work of VB and AC during this process and provided their knowledge on systematic reviews.

Details of ethical approval

None.

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Acknowledgment

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Table 1. Study characteristics and methodological quality of included studies

Citation	**Design; country; sample size**	**Participants**	**Intervention**	**Outcome**	**Risk of bias**
Adler et al. 1996[27]	Cluster RCT; USA; *n=50*	Seronegative women (*n=116*) with a child <36 months, shedding CMV and enrolled in 1 of 15 day-care centres in Richmond, Virginia, USA. 39 participants unavailable, 12 refused to participate and 12 excluded from the	*Education intervention (*E, *n=11):* Written and oral info + bi-weekly home visits to measure adherence *Education and adherence intervention (*A, *n=8)*: as above + bi-weekly visit to problem solve and reinforce adherence	Seroconversion: Controls: 47% E: 36.4% A: 25% P: 0% *P* < 0.29	RS: low AC: low BP: n/a BO: n/a IO: low SR: low CF: high

		analysis because child stopped shedding CMV after enrolment.	*Pregnant (*P, *n=14)*: written and oral info Control (C, *n*=17): basic info only		
Adler et al. 2004[20]	Cluster RCT; USA; *n= 166*	Mothers *(n=234)* who were either pregnant or attempting pregnancy and had a child < 36 months enrolled in 1 of 124 childcare centres, Central, Northern, Eastern Virginia, USA. 42 excluded as CMV-seropositive at enrolment, 26 failed to provide follow-up specimens.	*Intervention 1 (n= 92, child's shedding unknown):* written, oral and video info + adherence visits *Intervention 2 (n=23, child's shedding known*): written, oral and video + adherence visits *Control group (*C, *n=51):*	Seroconversion: Control: 7.8% Intervention : 7.8% *P*= 1 Pregnant: 5.9% Attempting pregnancy: 41.7% *P= .008*	RS: low AC: low BP: n/a BO: n/a IO: low SR: low CF: not assessable

			basic info only		
Citation	**Design/country/sample size**	**Participants**	**Intervention**	**Outcome**	**Risk of bias**
Valoup-Fellous et al. 2009[31]	Case series; France; *n = 5173*	Pregnant women *(n= 5312)* who had their first medical visit to an obstetric department between January 2005 and December 2007 and had been followed until end of pregnancy, 139 refused CMV screening.	Detailed oral and written hygiene information administered by obstetrician or midwife	Seroconversion: 0 - 12 WG: 0.42%, 12 - 36 WG: 0.19%, $P < 0.005$	CV: not assessable BO: n/a CF: low
Revello et al. 2015[32]	Interventional and observational controlled; Italy;	Pregnant women *(n= 4096)* undergoing genetic screening in an Italian hospital who have	*Intervention (n=331):* written and oral info + reinforcement + adherence	Seroconversion: Intervention: 1.2% Comparison: 7.6%	CV: low BO: n/a CF: low

	n = 646	frequent contact with young children (own child or working with children < 36 months) and who were either CMV-seronegative or had not tested for CMV immune status.	questionnaire *Comparison group (n=315):* women not tested or informed about CMV during pregnancy (serum sample stored)	delta=6.4%; 95% CI 3.2 - 9.6; $P < 0.001$	

Table 1. (continued)

Citation	**Design/country/sample size**	**Participants**	**Intervention**	**Outcome**	**Risk of bias**
Hughes et al. 2017[28]	RCT: USA; *n = 187*	Pregnant women *(n=223)* who were screened for CMV	*Intervention (n=124):* 5 minute video with hygiene teaching + take home	Behavioural compliance: Intervention: mean:	RS: low AC: low BP: n/a

		serology during prenatal care before 20 WG, 26 did not meet inclusion criteria, 1 miscarried, 4 withdrew, 1 crossed over to control, 1 crossed over to intervention.	calendar + weekly text message reminders *Control group (n=63):* standard care	7-point increase from 80.7 to 87.7, 95% CI 2.4-5.9 Control: 4-point increase from 79.7 to 84.1, 95% CI 5.9-8.4 Mean difference: 3.0, 95% CI , 0.8-5.2; *P* = 0.007	BO: n/a IO: low SR: low CF: low
Finney et al. 1993[29]	Pre-test Post-test; USA; *n = 11*	Mothers *(n=11)* who had a child <18 months enrolled in one of three day-care centres,	15 minute education session with a physician and written instructions	Hand washing and glove use increased. "Risky" behaviours	CV: high BO: not assessable CF: not

		Virginia, USA.		decreased: 14.4% - 5.1%	assessable
Price et al. 2014[30]	Pre-test Post-test; USA; *n = 809*	African-American *(n=404)* and Caucasian women *(n=405*), who had a child < 5 years and were either pregnant *(n=328)* or planning a pregnancy *(n=481).*	*Intervention 1 (n=404):* written info *Intervention 2 (n=405):* 5 minute video	Knowledge score: *Intervention 1 and 2:* 37% - 91%, *P* < 0.001	CV: high BO: not assessable CF: not assessable

RCT, randomised controlled trial; RS, random sequence generation (selection bias); AC, allocation concealment (selection bias); BP, blinding of participants (performance bias); BO, blinding of outcome assessment (detection bias); IO, incomplete outcome data (attrition bias); SR, selective outcome reporting (reporting bias); CV: control of confounding variables; CF: completeness of follow up data; n/a: not applicable; WG, weeks' gestation.

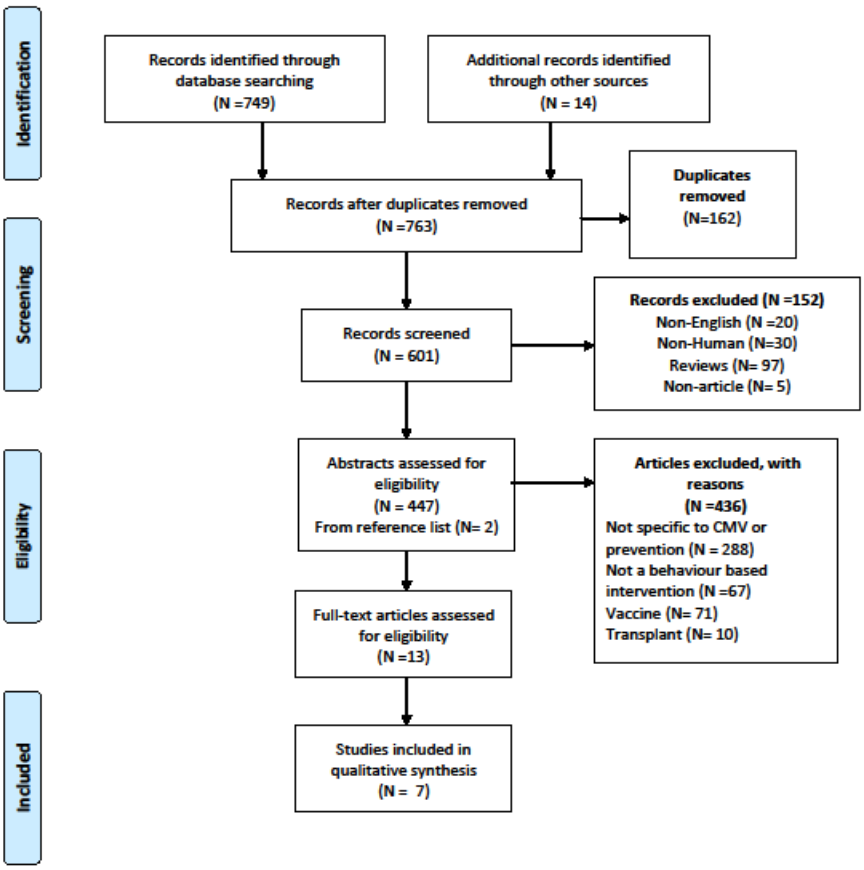

Figure1. PRISMA Flow Diagram