

# Screening of group B Streptococcus infection in pregnancy and neonatal outcomes in the province of Trento, Italy

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## SUMMARY

The study analyzes the trend of group B streptococcal (GBS) infection in pregnancy in the province of Trento, Italy, where a universal screening of GBS infection in pregnancy has been active for some time. Data from pregnant women who gave birth at local maternity units between 2015-2019 were obtained from birth attendance certificates (BAC), the main - and mandatory - source of information for monitoring pregnancies, births and neonatal health in Italy. The BAC used in the province of Trento acquires the results of a vast range of infections in pregnancy. The data collected from the BAC were integrated with those provided by the Hospital Information System (SIO). The occurrence of neonatal GBS infection was investigated on 2019 birth cohort, using the hospital discharge archive as an ancillary information source. Between 2015-2019, 20,905 pregnant women received care at maternity units of the province of Trento, Italy, of whom 25.5% were foreigners. The average coverage of GBS testing in pregnancy was 91.8% (95% CI 91.25-92.35) without significant variations from one year to the next. Test coverage varies in relation to maternity units and some socio-demographic characteristics of mothers. The average proportion of GBS positive cases over the study period was 21.0% (95% CI 20.7-21.3), a value that does not show statistically significant changes from one year to the next. The proportion of positive

cases appears uneven among the subgroups of pregnant women considered, even if the differences are not statistically significant. In the 2019 birth cohort, newborns to GBS-positive mothers had an excess of stillbirths, of those born with Apgar at 5 minutes <7 and hospitalized at birth. However, these excesses were not statistically significant. Intravenous Antibiotic Prophylaxis (IAP) was performed in 86.8% of births from GBS positive mothers who had an indication for IAP. IAP was inadequate in 7.4% of the GBS positive mothers. Postnatal evaluation of 783 live births to GBS positive mothers identified 3 cases of early neonatal GBS infection. The incidence of neonatal GBS infection over the whole series of live births is 0.71/1,000 (95% CI 0.56-0.86), 0.68/1000 (CI 95% 0.55-0.79) in Italians and 1.07/1000 (95% CI 0.45-1.65) in foreigners. Data collection on infections in pregnancy through BAC allows area-based assessment. The quality of the data recorded in the BAC can be considered satisfactory but it was necessary to access to other information sources. The local availability of various information sources should allow periodic audits and closer monitoring of neonatal GBS infection.

*Keywords:* Group B streptococcus infection, pregnancy, universal screening, neonatal infection, birth attendance certificate.

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## ■ INTRODUCTION

Group B streptococcus (*Streptococcus agalactiae* or group B beta hemolytic streptococcus) (GBS) is one of the many bacteria present within the body where, normally, it does not cause any problems [1]. An infection during pregnancy, with colonization of the gastrointestinal and/or genitourinary tract, occurs on average in one out of 4 pregnancies with wide variations in the prevalence between different countries [2, 3-11]. In pregnant women, GBS colonization can cause urinary infections, chorioamnionitis, endometritis or infectious complications from caesarean section. It can also be responsible for miscarriage or premature rupture of membranes which can lead to preterm birth [12-14]. A GBS colonization in pregnancy can involve a risk of transmission of the bacterium from mother to newborn during the passage through the birth canal, although in most cases this colonization does not result in serious consequences for the newborn. In any case, GBS represents one of the main causes of severe neonatal infection and especially in the presence of specific risk factors, neonatal colonization can cause invasive infections [2, 15]. These must be distinguished, on the basis of the time in which symptoms develop, in an early infection, with clinical onset within 7 days of birth and a late infection, with onset of symptoms from 8 days up to 3 months of life. The early form often manifests as sepsis, pneumonia, respiratory distress, while the late form, generally associated with an environmental contamination, manifests above all as meningitis, often with permanent outcomes [2, 15]. The Centers for Disease Control and Prevention (CDC) first published consensus guidelines on the prevention of perinatal group B streptococcal (GBS) disease in 1996 [16]. These guidelines, with subsequent amendments provide for universal screening for group B streptococcal infection in pregnancy and intrapartum antibiotic prophylaxis (IAP) in pregnant women who are GBS positive [17-19]. This procedure has proven to be more effective than the approach based on the presence of specific risk factors, in preventing GBS invasive neonatal disease, especially the early onset form [18, 20]. In many countries, including Italy, there is a universal screening of GBS infection in pregnancy, through the execution of a vaginal and rectal swab to be performed between the 36th and

37<sup>th</sup> week of gestation. In Italy, this procedure is one of the checks exempt from cost sharing and it is recommended by the national guidelines on physiological pregnancy [21]. In the province of Trento (north east Italy, 540.00 inhabitants as of 31 December 2019), the screening of GBS infection in pregnancy has been active for almost twenty years and the results of the vaginal and rectal swabs for the search for the presence of GBS have been recorded in the Birth Assistance Certificate (BAC) for fifteen years. Throughout Italy, the completion of this document by the healthcare professionals present at the time of the birth is mandatory by law [22]. This paper provides data on the prevalence of GBS colonization in the pregnant women who delivered at the maternity units of the province of Trento, Italy, between 2015 and 2019, and also evaluates the use of IAP and neonatal outcomes on newborn to GBS-positive mothers in the 2019 birth cohort.

## ■ PATIENTS AND METHODS

As recommended by the national guidelines for the assistance of physiological pregnancy, the GBS testing protocol operating in the province of Trento provides for a vaginal-rectal swab to be performed between the 36<sup>th</sup> and 37<sup>th</sup> week [21]. The swabs are performed, in the event of a full-term pregnancy, at the local family counselling centers. Two swabs (vaginal and rectal), are routinely performed by the clinicians before the digital examination and avoiding the use of the speculum when taking the vaginal sample. If there is a threat of preterm labor, a vaginal swab and a cervical swab are performed. Ampicillin is the drug of choice for IAP. However, it is not recommended for patients with scheduled caesarean birth due to the very low risk of transmission of GBS to the fetus/newborn [22]. In scheduled caesareans birth, prophylaxis is not done with ampicillin for GBS, but with a cephalosporin as operative prophylaxis. Ampicillin dosage, in case of premature rupture of the membranes, is initially 2g by intravenous infusion, then 1g every 6 hours until the onset of labor and then 1 g every 4h. If the woman is already in labor at hospital admission, the initial 2 g intravenously is given instead and then 1 g every 4 hours until delivery. In case of allergy to ampicillin, clindamycin (900 mg every 8 hours) is administered upon results

of susceptibility tests. In the event that a pregnant woman enters the hospital during the expulsion period and the result of the swab is not known, the GBS-positive woman protocol is used. The woman with premature rupture of the membranes and positive swab without contractions is induced immediately after the arrival of the entrance exams; while the woman with premature rupture of the membranes and negative swab without contractions is induced 24 hours after the rupture of the sac. We considered all assisted pregnant women, including those with GBS bacteriuria during ongoing pregnancy and those who previously gave birth to a child with invasive GBS disease. This is because the data entry criteria in the BAC do not allow for this type of differentiation. The identification of pregnancies at increased risk for vertical transmission of GBS is achieved using a culture-based approach. The result of the vaginal-rectal swab is generally recorded in the personal obstetric guide of the pregnant woman and systematically in the computerized archive of the BAC in all maternity units of the province of Trento. The BAC used in the province of Trento acquires more pregnancy-related parameters than is required by the ministerial template. More specifically, it also acquires information on antenatal serology screening for various infections and, in this particular case that for the ascertainment of GBS colonization. Registration in the BAC archive is the responsibility of the midwives present at the time of delivery. The criteria for the recording of vaginal-rectal swab results are the following: test not performed, negative test, positive test, results pending. For cases recorded in the BAC as results pending or positive test, we consulted and retrieved data from the hospital information system (SIO), an electronic repository used to store all the clinical information regarding both residents and non-residents who receive any service from the Provincial Health Service. The consultation of the SIO made it possible to ascertain the true positives cases. The SIO was also used to analyze the use of IAP amongst GBS positive pregnant and to ascertain the outcomes in newborn of GBS positive mothers. Access to the SIO was made by one of the authors (RR), expressly authorized for this task. We analyzed the coverage trend of vaginal-rectal swabs over time in all pregnant women assisted in all maternity units. Mean coverage is provided

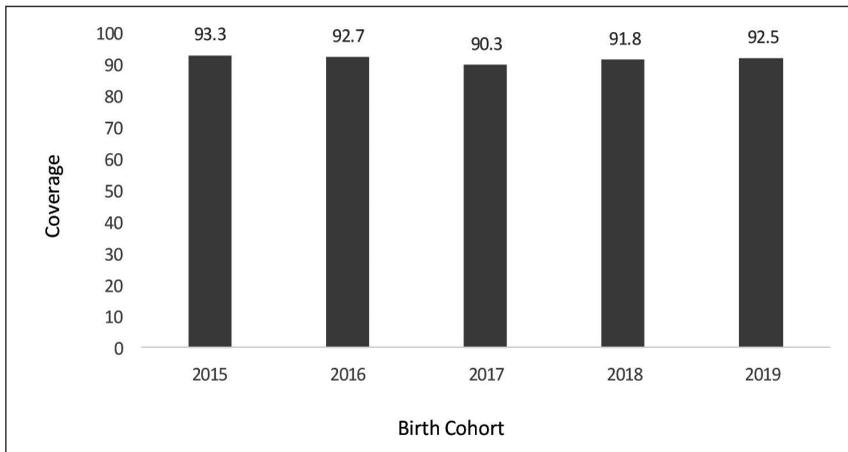
with 95% confidence intervals. The coverage was also evaluated in relation to the following maternal variables: age groups, nationality, educational degree, parity, gestational age, residence in or out the province of Trento, and, only for those residents in Trento province, the geographic area of residence: urban vs. rural. The proportion of positive GBS mothers is analyzed by birth cohorts and by specified variables, similar to those used for the analysis of test coverage. The mean proportion of GBS positive mothers and those for the individual specified variables are provided with 95% confidence intervals. The obstetric outcomes and the neonatal outcomes for GBS positive mothers were analysed for the 2019 birth cohort, by comparing them to those of negative mothers, using BAC as primary informative source. The statistical significance of the differences, for the variables compared, was analyzed with the chi-squared test or with the exact Fischer test, when necessary. The occurrence of any early or late neonatal invasive GBS infection of the newborns of a GBS positive mother was assessed at birth and up to the age of one year, using as primary informative source the hospital discharge forms archive (HDA). The cases with the following pathology codes ICD9 CM 771.8-771.89 were selected from HDA of live births in the year 2019 (4,203), with the additional code 041.02 in all diagnostic positions; the following ICD9 CM codes of procedure were also considered: 99.21 (injection of antibiotics) and 99.22 (injection of anti-infective agents) in all procedural positions (primary and secondary). The dataset thus obtained has been analyzed in detail on the SIO: for confirming a possible case of neonatal GBS infection and also for the evaluation of the use of IAP and its adequacy. The case of early or late neonatal GBS infection was defined by the cultural isolation (blood, urine, liquor) of the infectious agent.

## ■ RESULTS

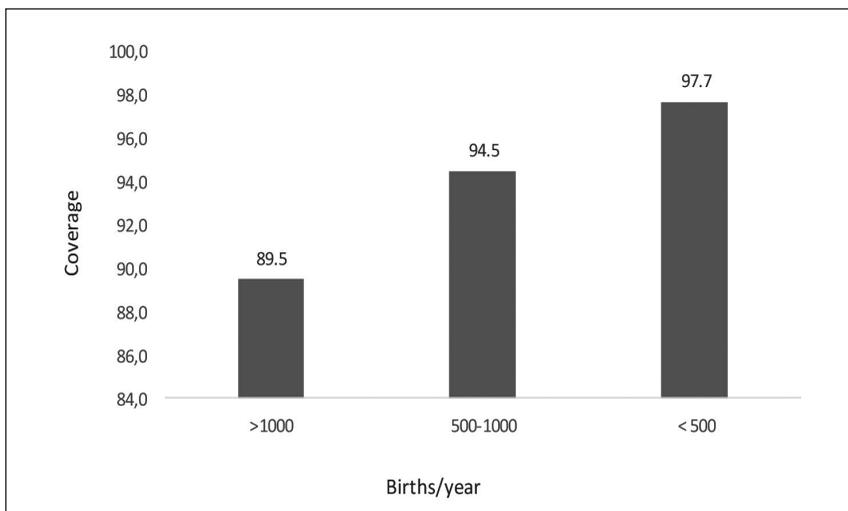
Between 01 January 2015 and 31 December 2019, 20,905 pregnant women received care at maternity units of the province of Trento, Italy. 5% of pregnant women were resident in other regions. The corresponding number of live births for the same period was 21,209. The average age of the pregnant women, in the study period, was 32,4 years and the percentage of those of foreign na-

tionality was 25,5%. The average coverage of GBS testing, considering all pregnant women, was 91.8% (95% CI 91.25-92.35) and it remains, for each year, above 90%, without significant variations from one year to the next (Figure 1). Test coverage was influenced by the annual number of births of maternity units (Figure 2); in fact, maternity units with a number of births up to 1000 per year (2 centers) has a higher coverage, with a statistically significant difference ( $p < 0.0001$ ) compared to maternity units with more than 1000 births/year (2 centers). The test coverage appears statistically significantly lower than expected in preterm births ( $p < 0.0001$ ), in mothers of age class  $\geq 35$  years ( $p < 0.01$ ), in foreign mothers

( $p < 0.01$ ), in mothers residing outside the province of Trento ( $p < 0.001$ ) and in mothers with low educational degree ( $p < 0.001$ ). There are no statistically significant differences in relation to the area of residence of women residing in the province of Trento and in relation to parity (Table 1). The average proportion of positive swab cases in the period under study was 21.0% (95%CI 20.7-21.3), a value that does not show statistically significant changes from one year to the next. The proportion of positive cases appears uneven among the subgroups of pregnant women considered, with non-statistically significant excesses, in pregnant women with term birth, in those aged  $>30$  years, in Italians, in pregnant women resident in the



**Figure 1 - Coverage of vaginal rectal screening for GBS infection in pregnant women assisted at the maternity units in the province of Trento. Trend 2015-2019.**



**Figure 2 - Coverage of vaginal rectal screening for GBS infection, by size classes of births of maternity units in the province of Trento. Period 2015-2019.**

**Table 1 - Province of Trento. Coverage GBS testing with CI 95% according selected maternal variables. Period 2015-2019.**

Variables	Coverage test (95% CI)
<i>Gestational age</i>	
Full-term pregnancy	94.3 (93.9-94.6)
Pre-term pregnancy	53.7 (50.9-56.4)
<i>Mother's age class</i>	
<25 y	91.9 (90.6-93.2)
25-29 y	92.4 (92.6-93.1)
30-34 y	93.0 (92.4-93.6)
35+ y	90.4 (89.7-90.7)
<i>Mother's citizenship</i>	
Italian	92.4 (91.9-92.8)
Foreign	90.2 (89.4-90.9)
<i>Mother's residence</i>	
In the province of Trento	92.0 (91.6-92.4)
Outside the province of Trento	88.2 (86.2-90.2)
<i>Geographical area of residence of women residing in the province of Trento</i>	
Urban area	90.4 (89.7-91.4)
Rural area	92.5 (92.3-92.7)
<i>Mother's educational qualification</i>	
Degree	92.7 (92.1-93.3)
High school	91.9 (91.4-92.4)
Middle school	90.2 (89.1-91.3)
Elementary School or none	85.7 (82.4-89.0)
<i>Parity</i>	
Primiparous	92.4 (91.6-93.0)
Multiparous	91.4 (90.8-91.9)

province who reside in rural areas and finally in the multiparous women. There is only one statistically significant excess: in residents outside the province (Table 2). Regarding the obstetric-neonatal outcomes, evaluated for the 2019 birth cohort, no statistically significant differences emerge between newborn from GBS positive vs. newborn to GBS negative mothers, in relation to the type of birth, gestational age and the presence of congenital malformations. In those born to a positive GBS mother, there are excesses in stillbirth, in the proportion of those born with Apgar at 5 minutes <7 and in hospitalized at birth. However, these

**Table 2 - Province of Trento. Proportion of GBS positive pregnant women and 95% CI according to selected maternal variables. Period 2015-2019.**

Gestational age	% GBS positive cases	CI 95%
Pre-term	16.4	(14.4-18.4)
Full-term	21.2	(20.9-21.5)
<i>Mother's age class</i>		
<25 y	19.3	(17.8-20.8)
25-29 y	19.6	(18.5-20.7)
30-34 y	21.5	(20.7-22.3)
35+ y	21.8	(21.0-22.6)
<i>Mother's citizenship</i>		
Italian	21.3	(21.0-21.6)
Foreign	20.2	(19.3-20.9)
<i>Mother's residence</i>		
Province of Trento	20.9	(20.4- 21.3)
Outside Province of Trento	23.4	(22.2-24.4)
<i>Geographical area of residence of women residing in the province of Trento</i>		
Urban	17.5	(16.3-18.7)
Rural	21.8	(21.0-22.6)
<i>Mother's educational qualification</i>		
Degree	20.8	(20.3-21.3)
High school	21.1	(20.5-21.7)
Middle school	21.4	(20.6-22.2)
Elementary/None	19.6	(18.6-20.6)
<i>Parity</i>		
Primiparous	20.2	(19.7-20.8)
Multiparous	21.6	(21.1-22.1)

excesses are not statistically significant (Table 3). IAP was performed in 86.8% of births from GBS positive mothers (680 cases), no cases born from a scheduled caesarean birth have been treated with IAP. In 2 cases (two precipitated deliveries) no prophylaxis is documented and in 50 cases (7.4%) (2 precipitated deliveries, 23 vaginal and 25 caesarean deliveries in labor) an IAP inadequate for timing and/or dosage is reported by the SIO. The totality of cases treated by an inadequate IAP are registered in the spoke maternity units with up to 1,000 live birth/year. Access to the SIO made it possible to identify about 15% of cases of antibiot-

**Table 3 - Province of Trento. Obstetric-neonatal outcomes in newborn to GBS positive mothers vs newborn to GBS negative mothers. Birth cohort 2019.**

Parameters	Newborn to GBS positive mothers (783 cases)	Newborn to GBS negative mothers (3,430 cases)
<i>Delivery mode</i>		
Vaginal	79.2%	77.1%
Scheduled caesarean section	11.0%	12.0%
Caesarean delivery in labor	3.4%	5.0%
Operative vaginal delivery	6.1%	5.6%
Kristeller	0.5%	0.2%
<i>Pre-term newborn</i>	3.9%	5.2%
<i>Stillbirth</i>	3.8/1.000	1.3/1.000
<i>Congenital anomalies</i>	1.3/1.000	4.0/1000
<i>Average birth weight</i>	3290 g	3303 g
<i>Low birth weight (&lt;2500 g)</i>	3.4%	5.1%
<i>Apgar 5 min &lt;7</i>	2.0%	1.5%
<i>Hospitalization at birth</i>	13.9%	11.6%
<i>Exclusive maternal breastfeeding</i>	82.6%	81.1%

ic prophylaxis that were not reported in the HDA. Postnatal evaluation of 783 live births from a GBS positive mother identified 3 cases of early neonatal GBS infection (two males and one female) and no cases of late neonatal infection. These three cases were inadequately treated with ampicillin. These three cases were born at term, two of which were from an Italian mother and one from a foreign one. The observed incidence of neonatal GBS infection over the whole series of live births is 0.71/1,000 (95% CI 0.56-0.86), 0.68/1000 (CI 95% 0.55-0.79) in Italians and 1.07/1000 (95% CI 0.45-1.65) in foreigners. The cases were transferred to the Neonatal Intensive Care Unit of the Santa Chiara Hospital in Trento, treated effectively and discharged at home, after an average hospital stay of 8 days.

## ■ DISCUSSION

The BAC represents, in Italy, a current mandatory information flow on assistance in pregnancy and childbirth with respect to which the individual regions/autonomous provinces have the opportunity to collect data on additional variables other than those provided for by the ministerial model [23]. In the province of Trento, Italy, for about 20 years, data on serological screening and bacteriological tests for infections in pregnancy

have been collected through the BAC. This allows an assessment by area rather than by centers, similarly to what has already been reported, for the Italian level, in the Emilia-Romagna region. An overall report on the surveillance of infections in pregnancy through the BAC in the province of Trento, for the period 2007-2014, was provided by our previous study [24]. However, this study represents our first in-depth evaluation of GBS infection in pregnancy. As with all current flows, it must be assumed that the prevalence estimates of any condition may be affected by the level of completeness and accuracy of the data recording in the BAC, an instrument whose aims are not primarily those of research and in particular of clinical research. In the province of Trento, however, we also have the opportunity to have the SIO which allows on the one hand to validate the data transmitted by the BAC and on the other to retrieve analytical information relating to both the mother and the newborn and which as such are not subject to ordinary registration in the BAC. The combined use of these tools can therefore be of help both in the epidemiological field and in the field of clinical research. The adopted linkage procedures between current flows are unfortunately not inferable to the national level due to regulatory limits relating to data confidentiality assurance. However, the use of the SIO remains

onerous, considering that it does not allow data export, but the reading or printing of documents or reports such as the letter of discharge. Given the sensitivity of the data, access to the SIO must also take place in a manner aimed at ensuring the maximum possible confidentiality. The coverage of the GBS testing is, in the period under study, always greater than 90%, a value consistent with what was reported in our previous overall study and, as regards specifically the GBS, higher than that reported by a previous national survey by the National Institute of Health and other regional studies [3, 5, 24, 25]. Coverage of GBS testing is higher in term births and in spoke maternity units, as reported by a previous Italian work [5]. This latter aspect could be explained by a possible greater availability of time by the operators of the maternity units in spoke centers. The test coverage also varies in relation to some socio-demographic characteristics of pregnant women. The data may express the existence of some inequality in access to the test even if, the variability in coverage for at least some of the covariates analyzed, could be more the result of some deficiency in recording the data in the BAC than the expression of a real difference. Differences in test coverage may also be due to clinical characteristics of the pregnant women which cannot be registered by the BAC. The prevalence of GBS positive pregnant women stands at 21%, a constant value over the study period and consistent with our previous overall study [24]. The prevalence of GBS positive cases appears to be higher than that reported by previous Italian studies, and which is between 7.9-19.7, although substantially in line with European studies [4, 5, 26-30]. The prevalence of positive cases increases with the age of pregnant women but in any case, the distribution of positivity for the analyzed covariates does not show statistically significant differences, as per previous Italian study [31]. The higher positivity reported in pregnant women residing outside the province of Trento could be entirely coincidental, also considering the scarce consistency of this series. With regard to obstetric-neonatal outcomes, assessed on the basis of data from BAC, no significant differences emerge between those born to positive and negative GBS mothers. In the first category there are excesses regarding stillbirth and hospitalization at birth, but these are not statistically significant, as reported by previous Italian stud-

ies [3-5]. IAP was carried out in about 87% of the births from a GBS positive mother and this estimate was made possible by having the data from the SIO, taking also into account the under-registration and sometimes inaccurate registration of this data in the HDA database. The proportion of subjects receiving IAP appears to be higher than that reported by previous Italian studies [3, 5, 32-34]. IAP is not carried out in scheduled caesarean births, due to the very low risk of transmission of GBS to the fetus/newborn and this is recorded in all provincial maternity units [22]. However, a similar homogeneity between maternity units does not appear if the adequacy of the IAP is considered. In 7.4% of the births of GBS positive mothers with indication for IAP, the SIO allows to document an inadequacy of the treatment either for dosage or for duration/timing of the infusion. All these cases are concentrated in the peripheral maternity units or spoke centers, where, moreover, the coverage of the GBS colonization test is higher. However, the proportion of inadequate IAP reported in our study seems lower than that reported by other previous Italian studies [3, 32, 33]. The 3 documented cases of early neonatal GBS infection provide an incidence equal to 0.71/1,000 live births, a value that is slightly higher, but still in line with the values reported by previous Italian and international studies [2, 3, 5, 34-38]. In all three of these cases, born in peripheral maternity units, IAP was inadequate. This leads to reiterating the importance of the adequacy of IAP for the purpose of preventing neonatal GBS disease, in particular early onset disease [2, 32, 39]. Given the use of IAP, a possible risk of induction of resistance and an increase in neonatal infections by bacteria other than GBS remains to be considered in any case [2, 15, 40]. In conclusion, the local availability of current information flows, used in an integrated way, can facilitate an assessment of the quality of care and indicate areas with priority for intervention. Our study would indicate the need to homogenize the IAP protocol among the maternity units. A real ability to evaluate the efficiency and effectiveness of healthcare services cannot be achieved without enhancing the current healthcare information flows and improving collaboration between clinical areas and epidemiology services. Periodic checks of the management criteria and of the outcomes of infections in pregnancy would be de-

sirable. These could become more relevant if the registration of infections in pregnancy through the BAC also took place in other regions.

### Conflicts of interest

None

### Funding

None

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