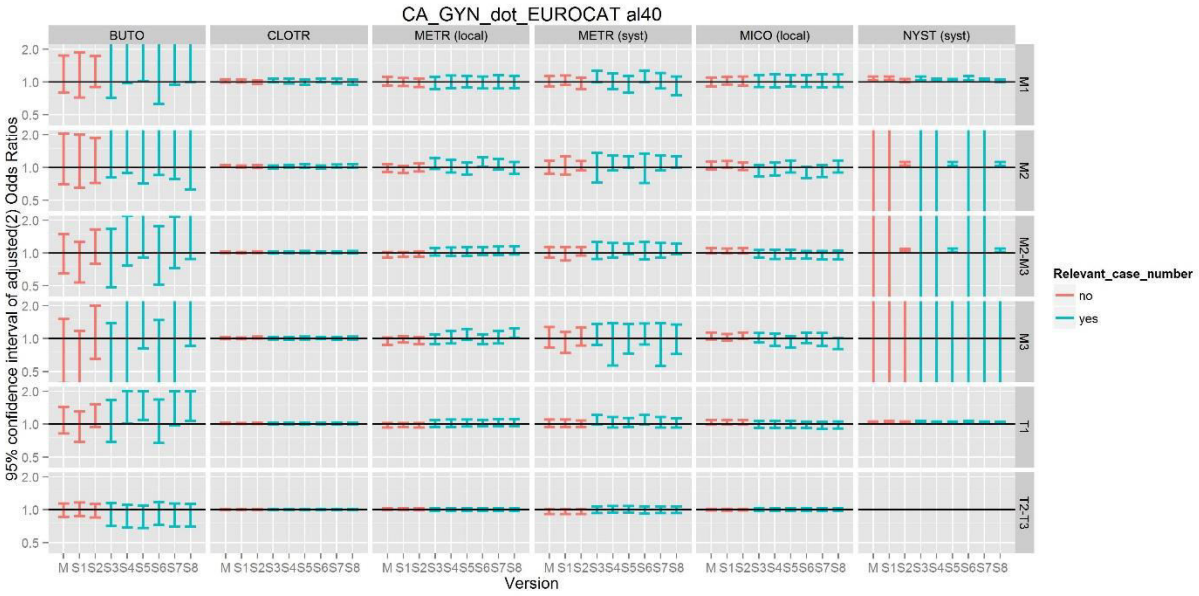
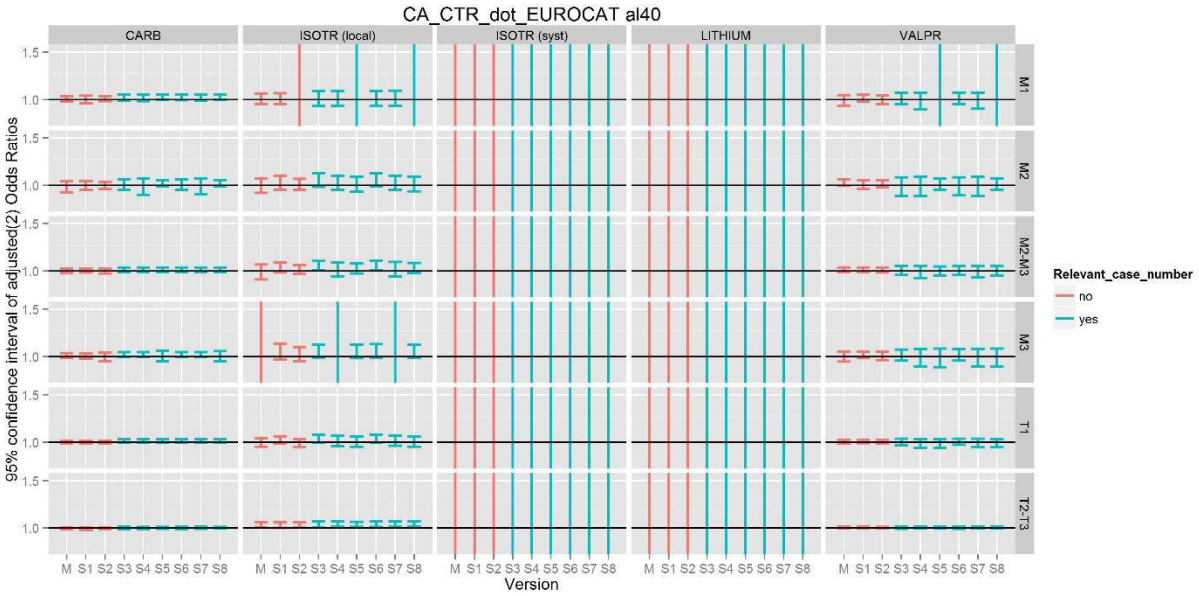

CA_GYN_dot_EUROCAT al40
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes


CA_CTR_dot_EUROCAT al40
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes

15.3.13. Digestive system, "other congenital malformations of tongue" (Custom Q383)

The custom Q383 code group has been defined as any reported ICD code in the Q383 range.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	4803	9.73 *
Excluding single outpatient reports (S3-S5)	1460	2.96 *
Excluding all outpatient reports (S6-S8)	1395	2.83 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		1.14 **

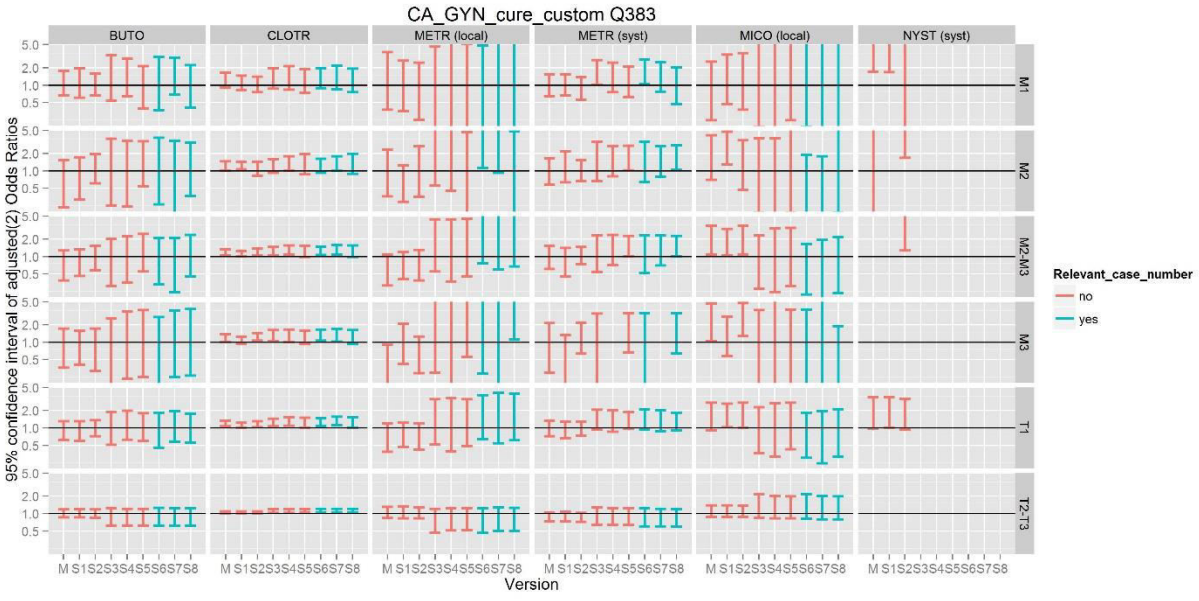
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

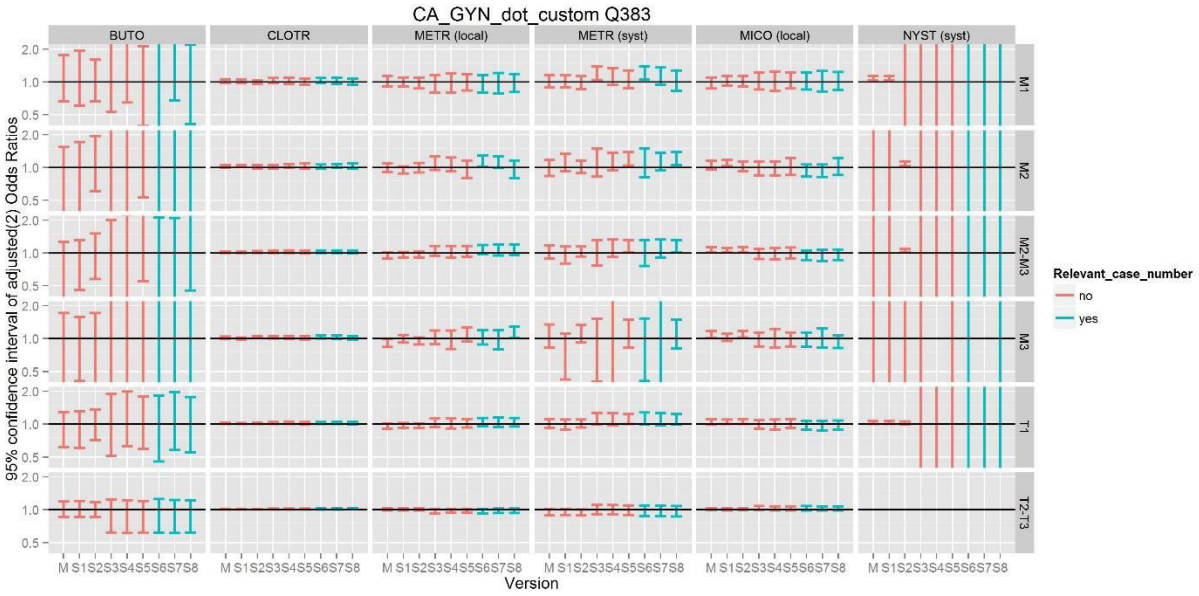
Based on the above numbers, single outpatient reports may be unreliable for the analysis of this anomaly; hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group. The under-reporting to the national registry is substantial, probably reflecting the relatively mild nature of this congenital defect.

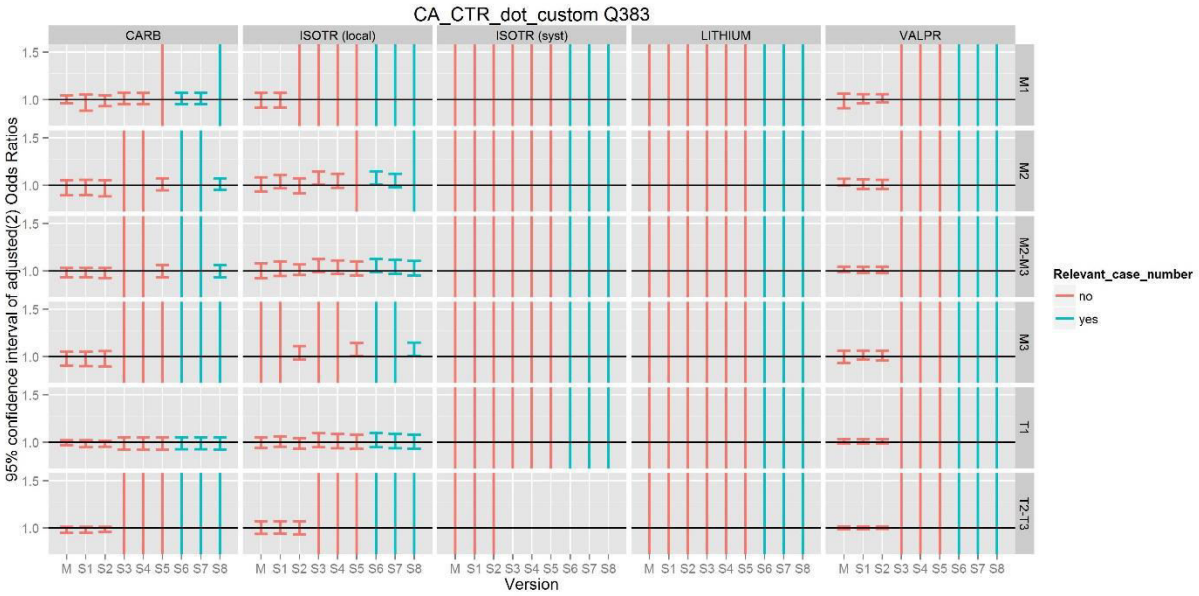
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.L. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.L. 95% confidence intervals of odds ratios of drug exposure in the Q383 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_custom Q383
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1S2S3S4S5S6S7S8
Version
Relevant_case_number
no
yes


CA_CTR_dot_custom Q383
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes

15.3.14. Digestive system, other (Custom RG03)

The custom RG03 code group has been defined as any reported al40 code except for Q383.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	1872	3.79 *
Excluding single outpatient reports (S3-S5)	1444	2.93 *
Excluding all outpatient reports (S6-S8)	1369	2.77 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		2.59 **

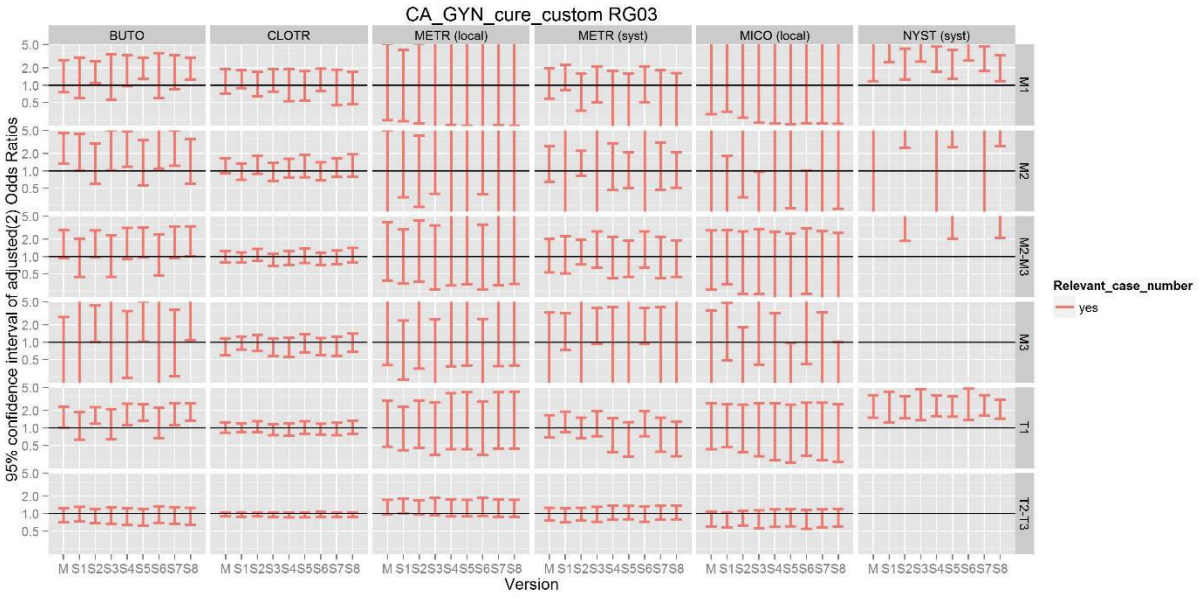
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

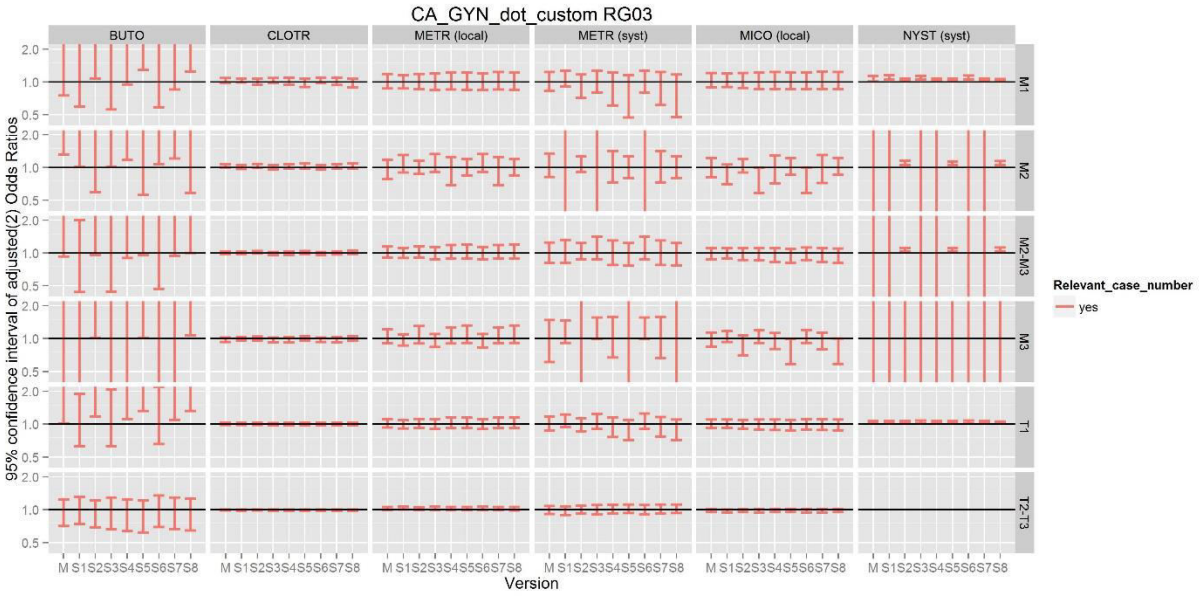
Based on the above numbers, the exclusion of single or all outpatient reports did not meaningfully reduce the number of RG03 cases in the study. The observed rate is consistent with the national statistics (assuming some underreporting of outptient cases to the registry). Acordingly, the main and sensitivity analyses have similar relevance for the analysis of this code group.

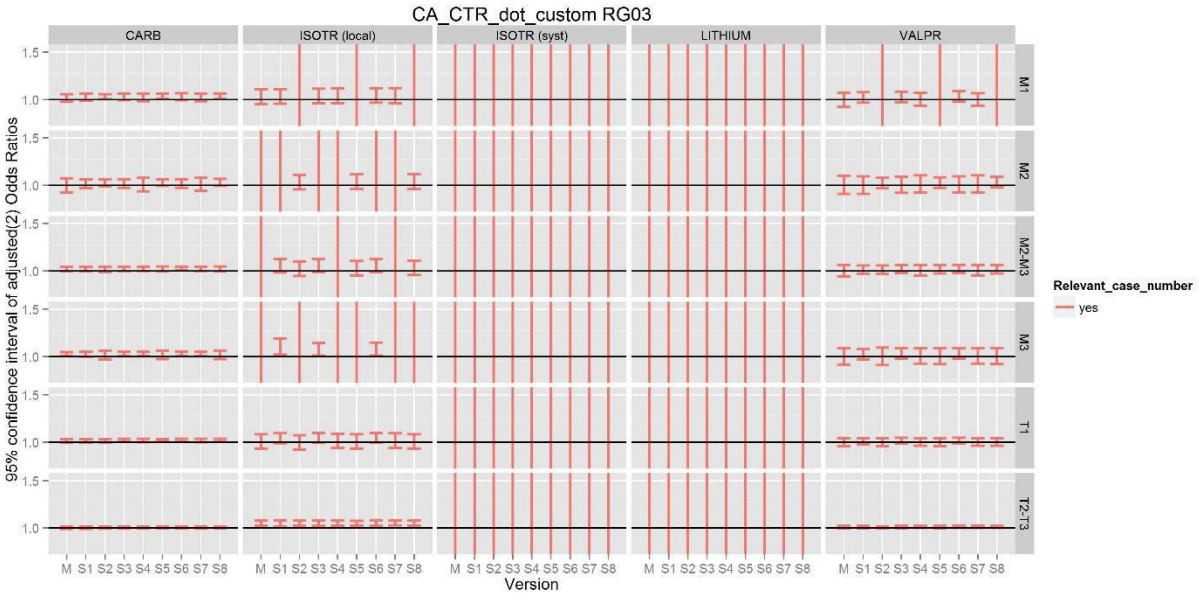
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.M. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.M. 95% confidence intervals of odds ratios of drug exposure in the RG03 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_custom RG03
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
yes


CA_CTR_dot_custom RG03
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
yes

15.3.15. Abdominal wall defects (EUROCAT al49)

The EUROCAT al49 code group has been defined as any report of Q792, Q793, and/or Q795 ICD codes.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	250	0.51 *
Excluding single outpatient reports (S3-S5)	184	0.37 *
Excluding all outpatient reports (S6-S8)	179	0.36 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		0.37 **

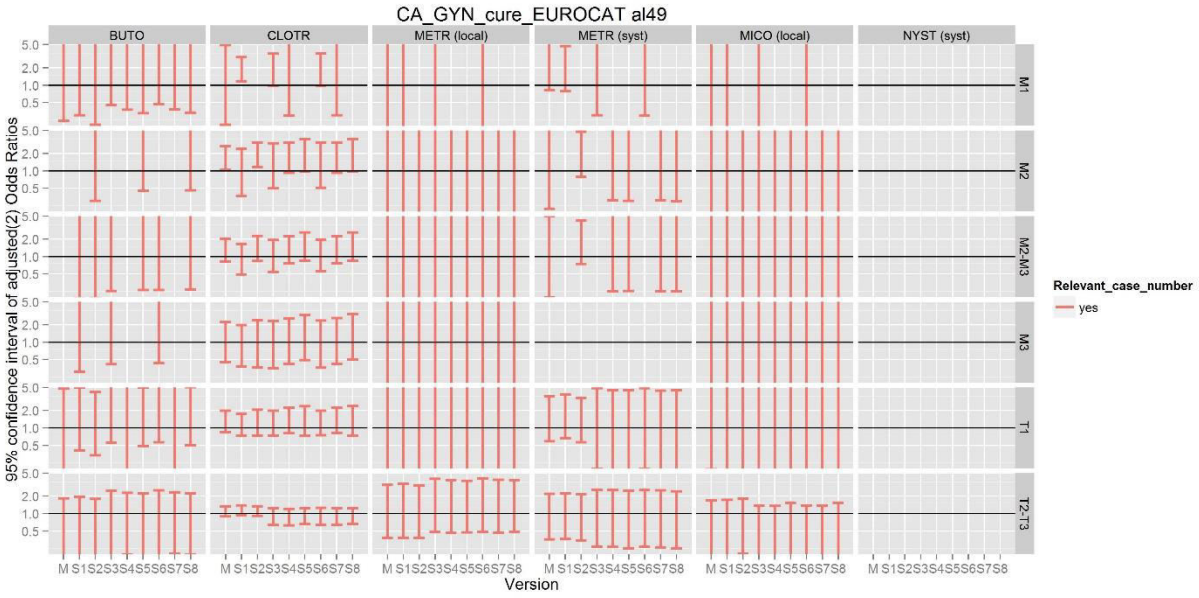
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

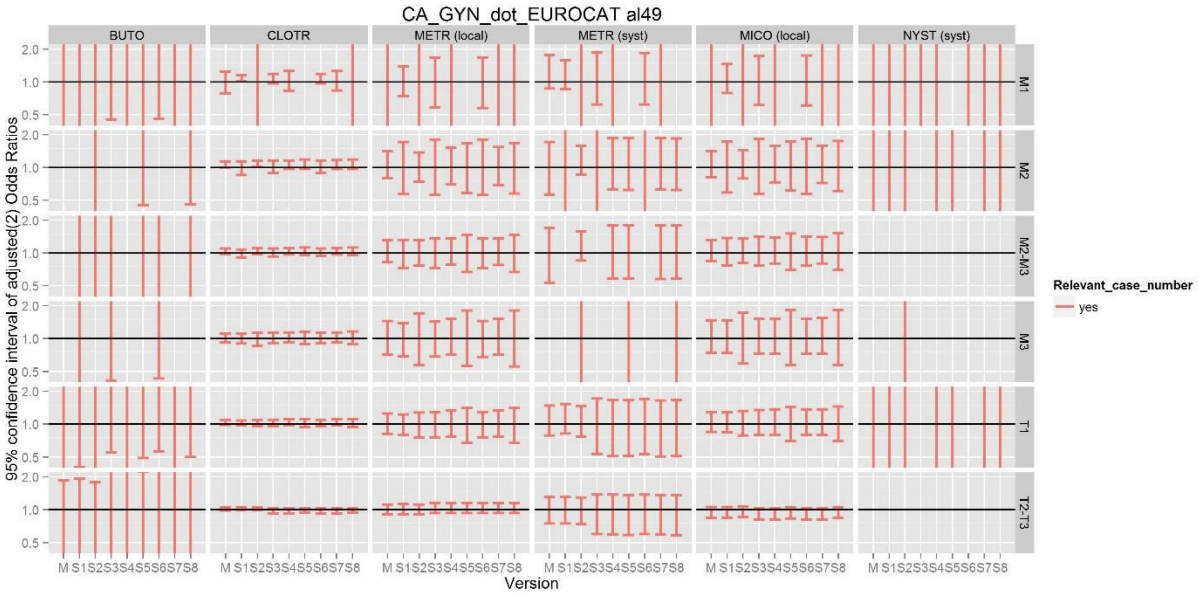
Based on the above numbers, the exclusion of single or all outpatient reports did not meaningfully reduce the number of al49 cases in the study. The observed rate is consistent with the national statistics (assuming some underreporting of outptient cases to the registry). Acordingly, the main and sensitivity analyses have similar relevance for the analysis of this code group.

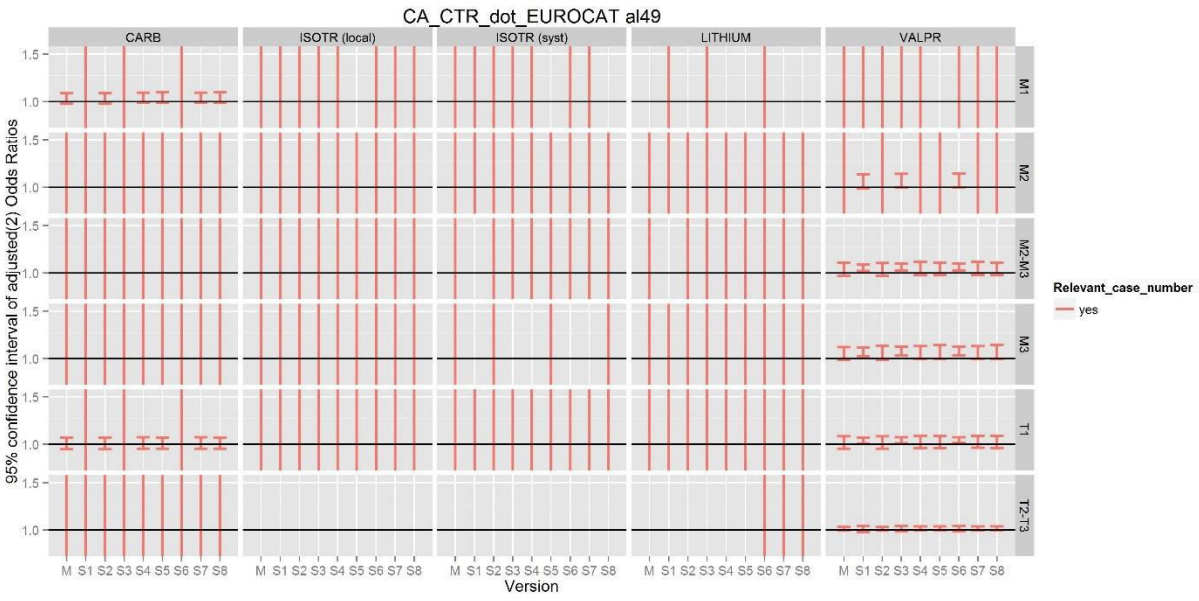
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.N. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.N. 95% confidence intervals of odds ratios of drug exposure in the al49 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al49
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1S2S3S4S5S6S7S8
Version
Relevant_case_number
yes


CA_CTR_dot_EUROCAT al49
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
yes

15.3.16. Abdominal wall defects, and/or disease indicative interventions (Custom RG04)

The custom RG04 code group has been defined as any report of Q792, Q793, Q795 ICD codes and/or disease indicative interventions (OENO 55340, 55350, 55358, 55359, 55360, 55361, 55369) in the first 3 years after birth (note the longer follow-up period in this analysis). For justification and details, please see Protocol Amendment 2, Annex 3.1.4.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	974	1.97 *
Excluding single outpatient reports (S3-S5)	856	1.73 *
Excluding all outpatient reports (S6-S8)	850	1.72 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		0.37 **

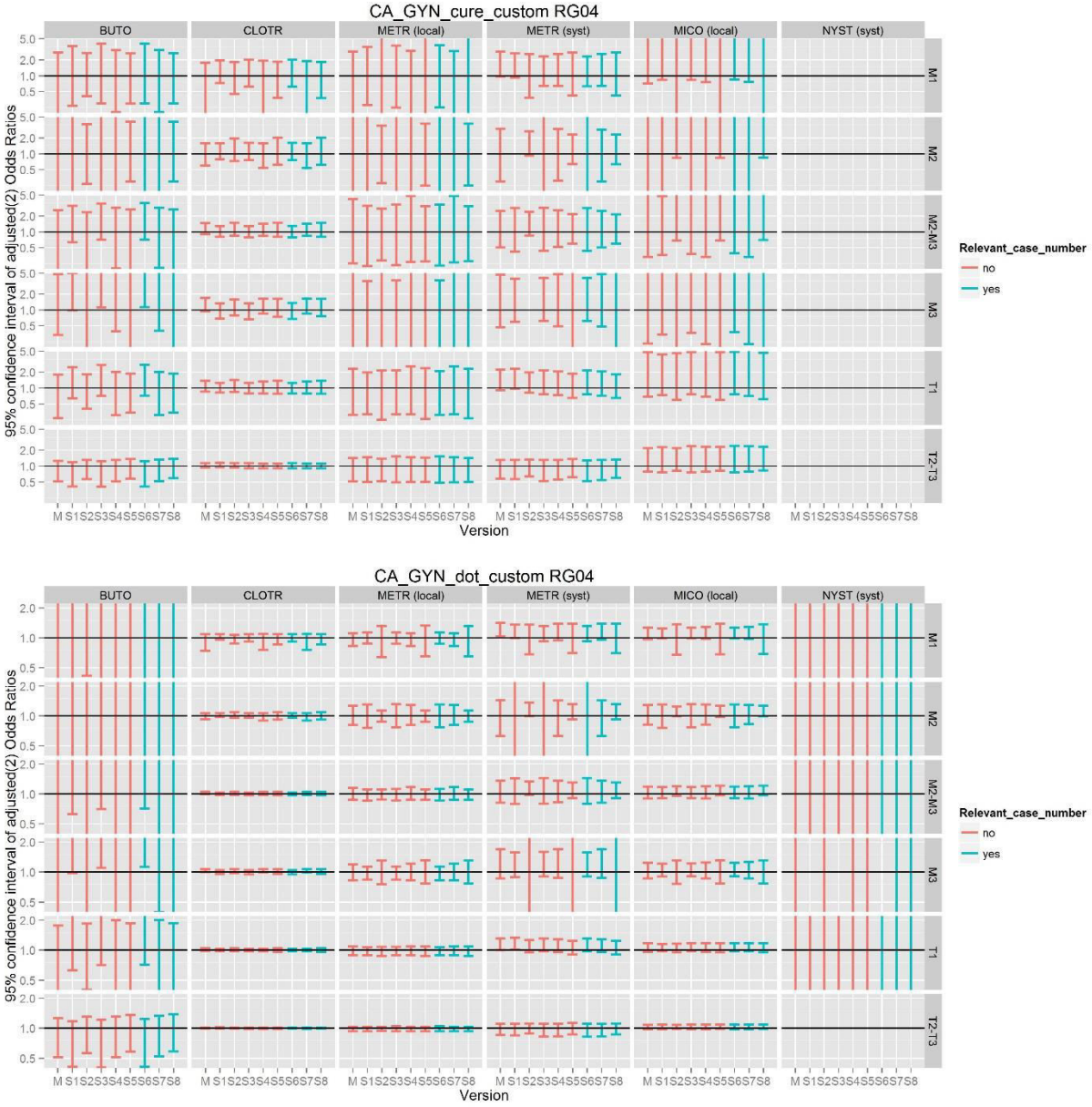
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

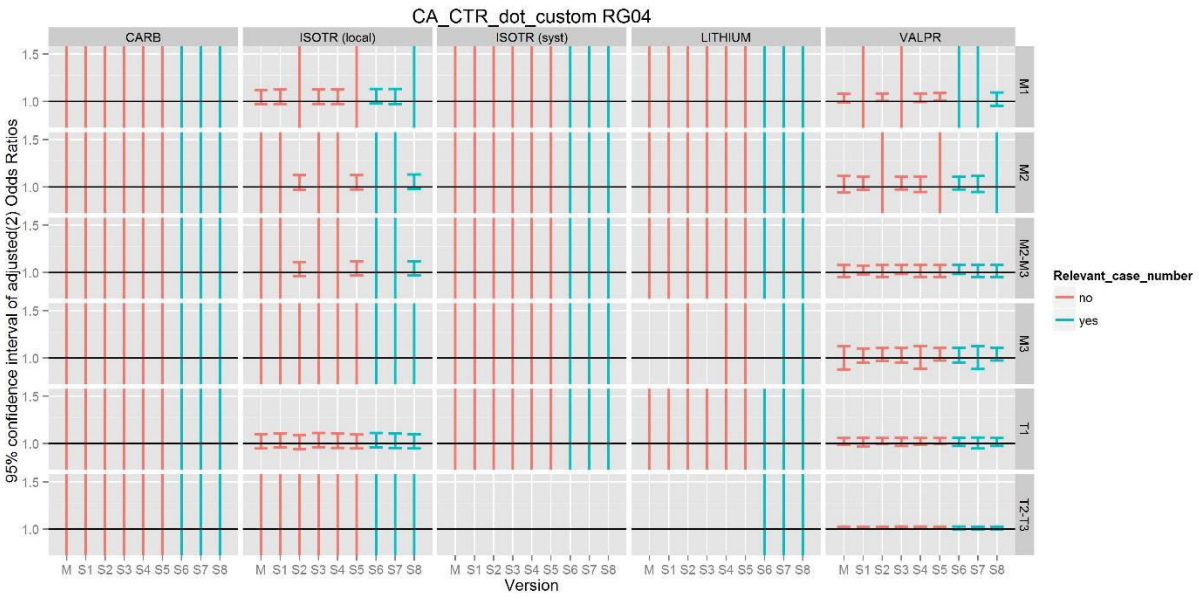
Based on the above numbers, the exclusion of single or all outpatient reports did not meaningfully reduce the number of RG04 cases in the study. The observed rate is about 5 times higher than the national statistics (assuming substantial underreporting of these cases to the registry). Acordingly, sensitivity analyses S6-S8 have the highest relevance for the analysis of this code group. Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.O.

For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.O. 95% confidence intervals of odds ratios of drug exposure in the RG04 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_CTR_dot_custom RG04
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
1.5
1.0
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes

15.3.17. Urinary (EUROCAT al52)

The EUROCAT al52 code group has been defined as any reported ICD code in the Q60-Q64, and Q794 ranges.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	24,767	50.18 *
Excluding single outpatient reports (S3-S5)	10,217	20.70 *
Excluding all outpatient reports (S6-S8)	6598	13.37 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		4.27 **

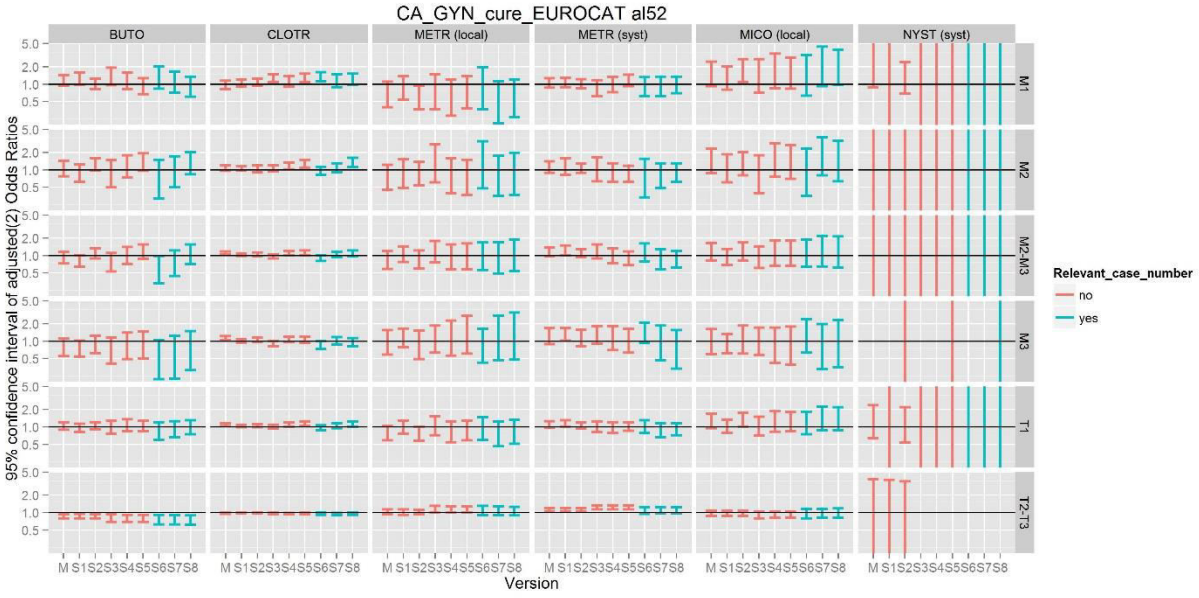
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

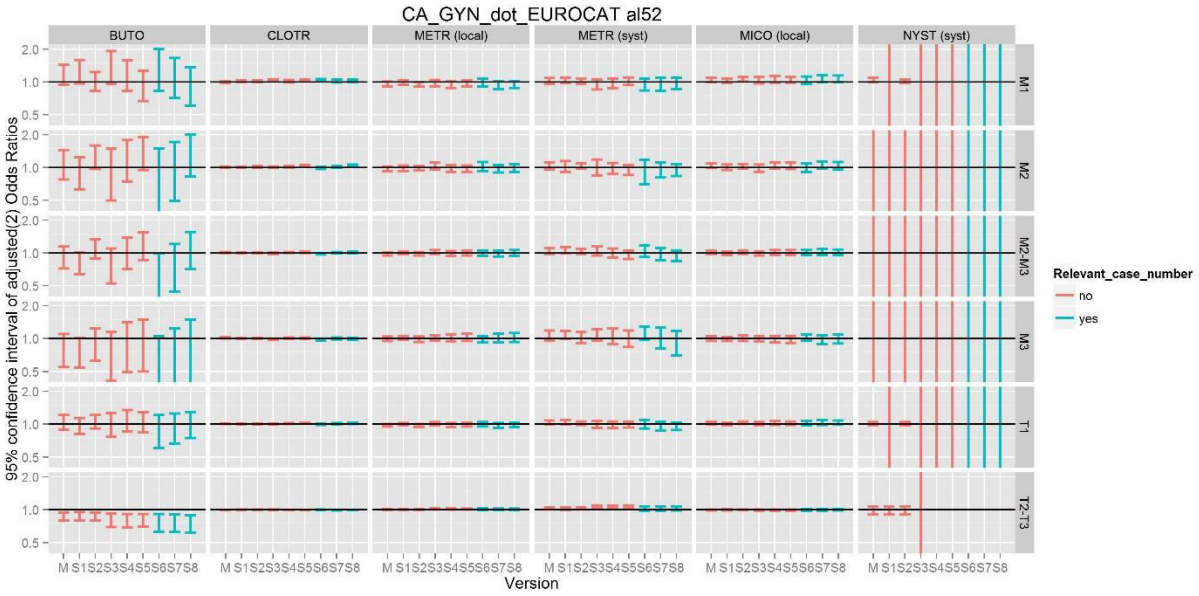
Based on the above numbers, outpatient reports may be unreliable for the analysis of congenital urinary anomalies; hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group. The under-reporting of inpatient cases to the national registry is substantial.

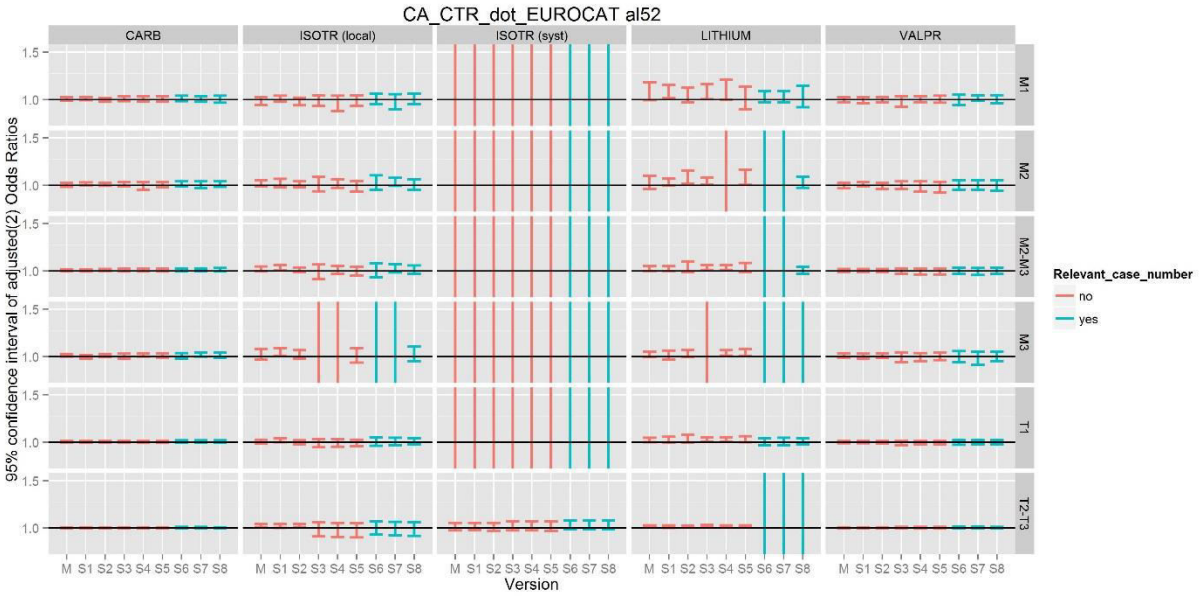
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.P. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.P. 95% confidence intervals of odds ratios of drug exposure in the al52 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al52
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1S2S3S4S5S6S7S8
Version
Relevant_case_number
no
yes


CA_CTR_dot_EUROCAT al52
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes

15.3.18. Congenital hydronephrosis (EUROCAT al55)

The EUROCAT al55 code group has been defined as any reported ICD code in the Q620 range.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	1150	2.33 *
Excluding single outpatient reports (S3-S5)	621	1.26 *
Excluding all outpatient reports (S6-S8)	412	0.83 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		0.31 **

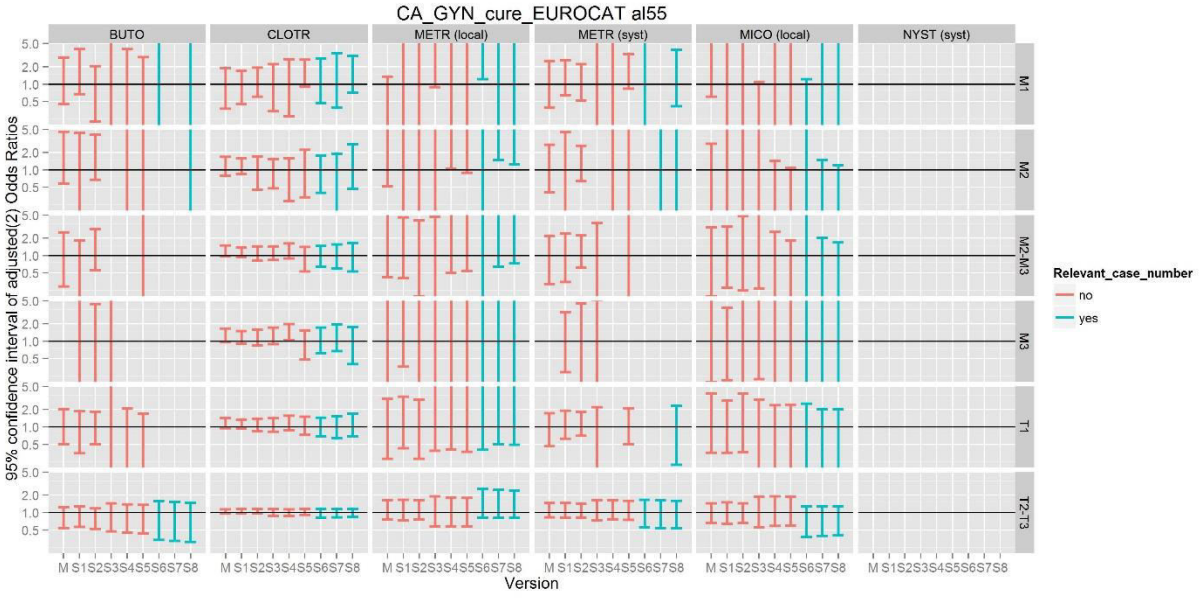
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

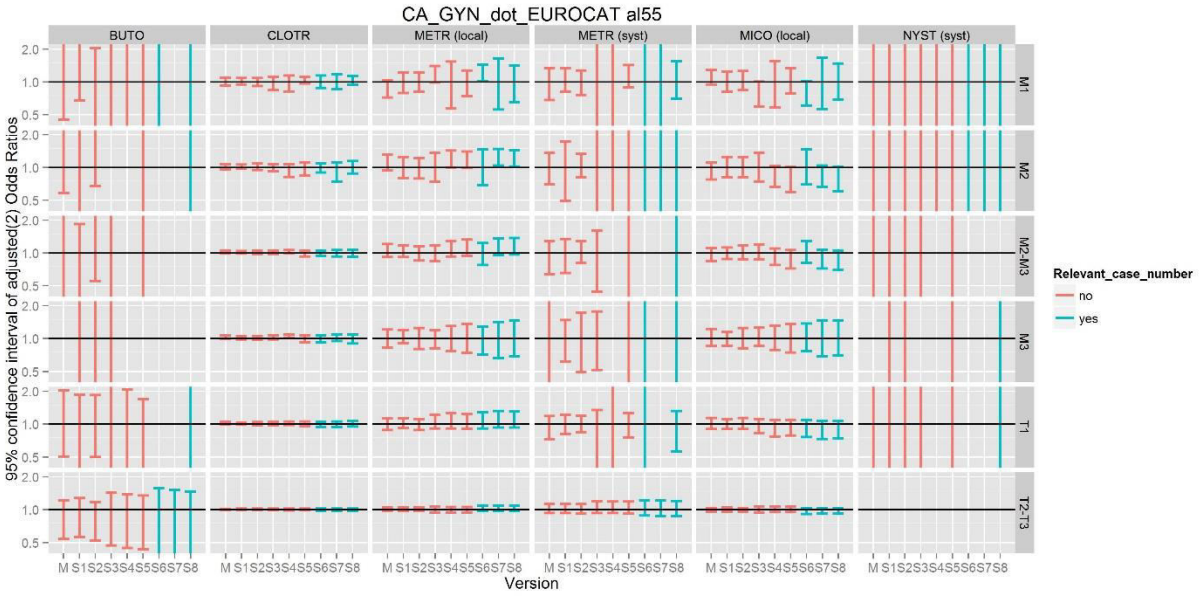
Based on the above numbers, outpatient reports may be unreliable for the analysis of congenital hydronephrosis; hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group. The under-reporting of inpatient cases to the national registry is substantial.

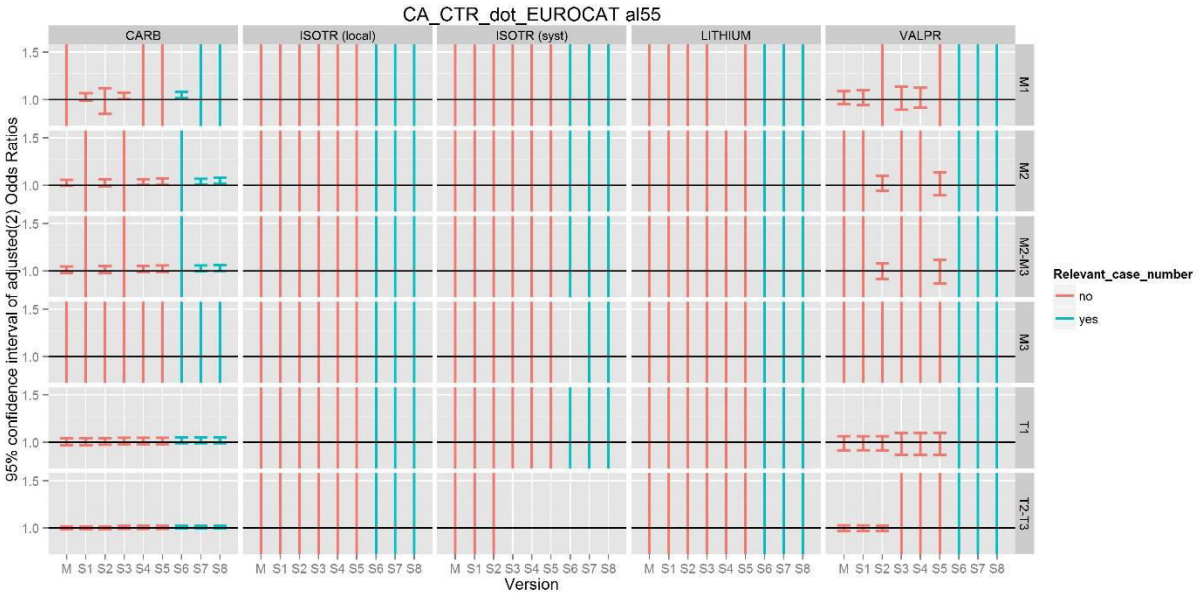
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.Q. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.Q. 95% confidence intervals of odds ratios of drug exposure in the al55 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al55
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes


CA_CTR_dot_EUROCAT al55
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes

15.3.19. Congenital malformation of kidney, unspecified (Custom Q639)

The custom Q639 code group has been defined as any reported ICD code in the Q639 range.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	16,019	32.46 *
Excluding single outpatient reports (S3-S5)	4390	8.89 *
Excluding all outpatient reports (S6-S8)	2056	4.17 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		1.80 **

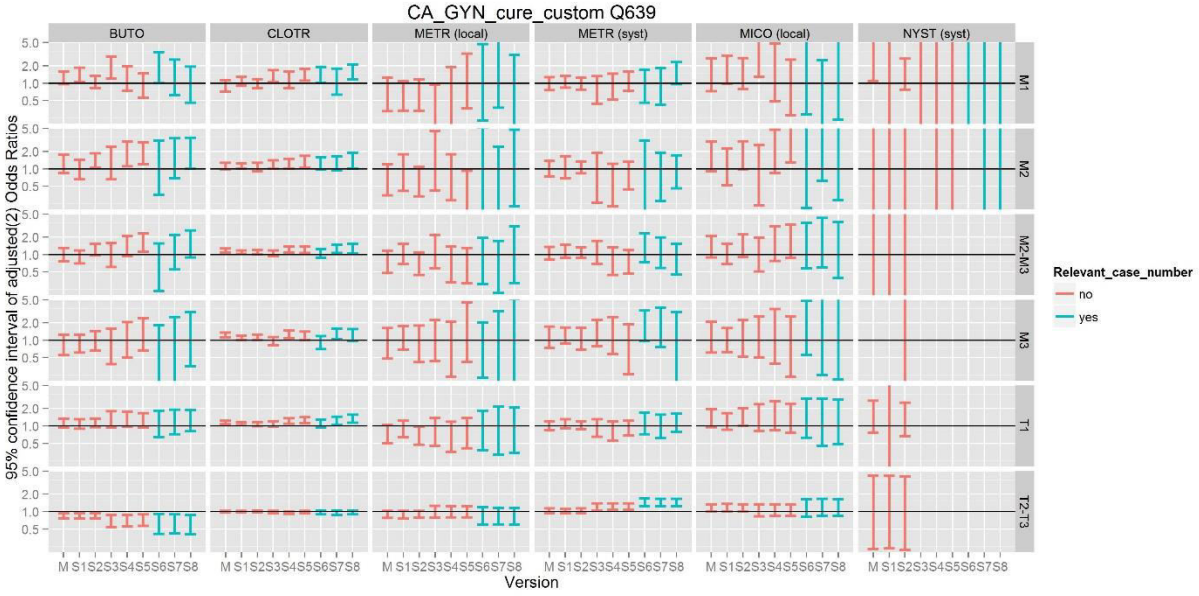
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

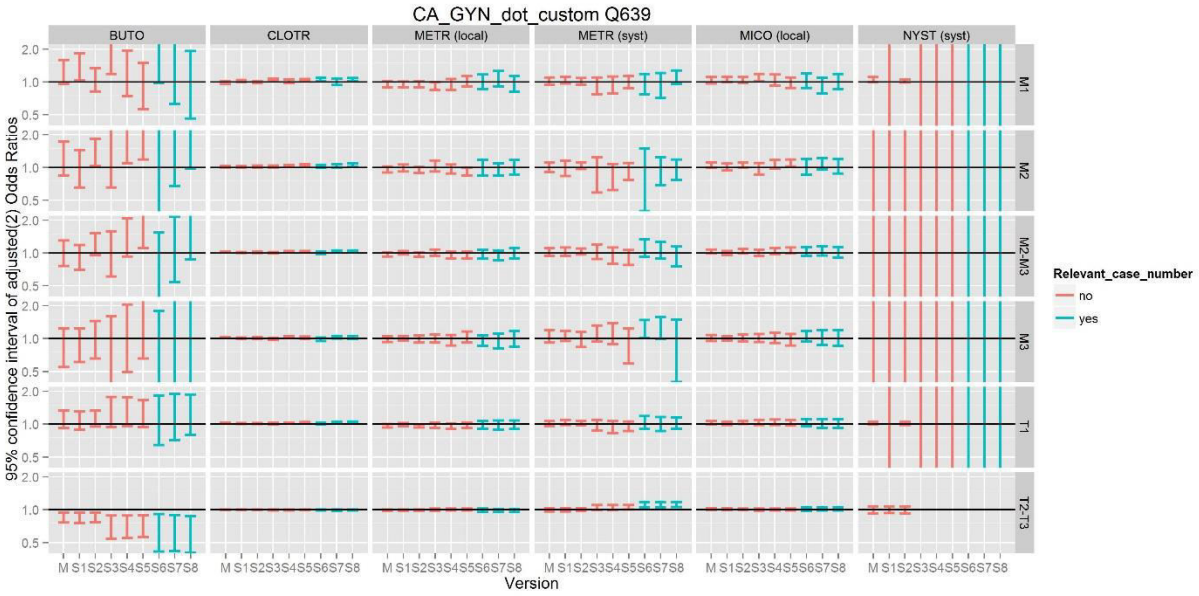
Based on the above numbers, outpatient reports may be unreliable for the analysis of this anomaly category; hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group. Note the substantial over-reporting of cases to the OEP database – due to the unspecific meaning of this code, part of the OEP reported cases may not represent severe/true congenital anomalies.

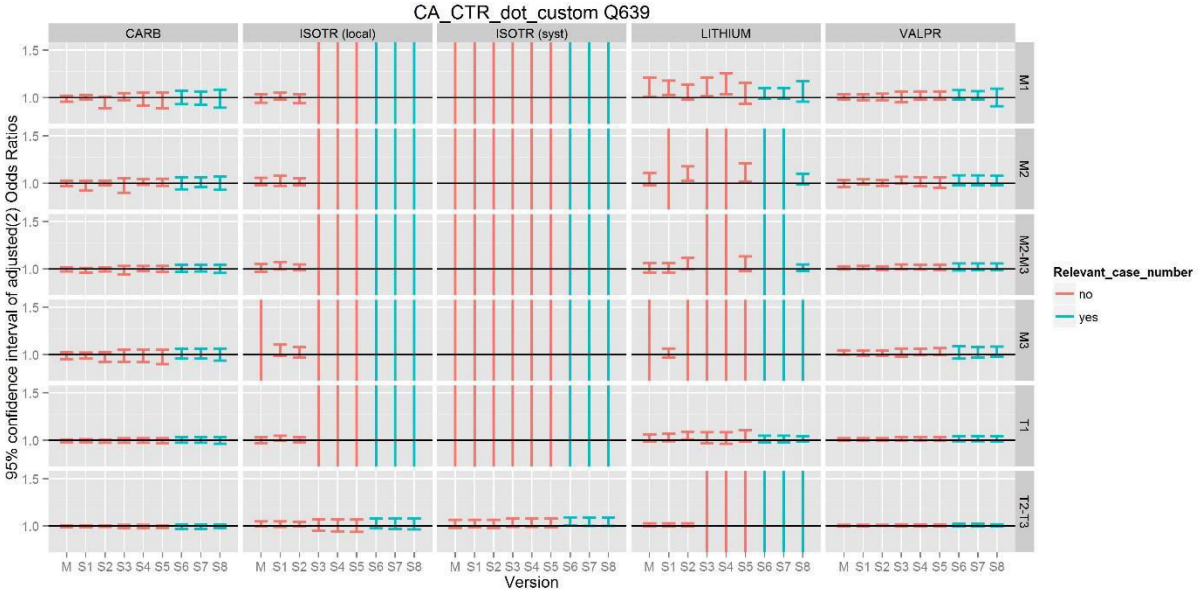
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.R. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.R. 95% confidence intervals of odds ratios of drug exposure in the Q639 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_custom Q639
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes


CA_CTR_dot_custom Q639
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes

15.3.20. Other obstructive defects of renal pelvis and ureter (Custom Q623)

The custom Q623 code group has been defined as any reported ICD code in the Q623 range.

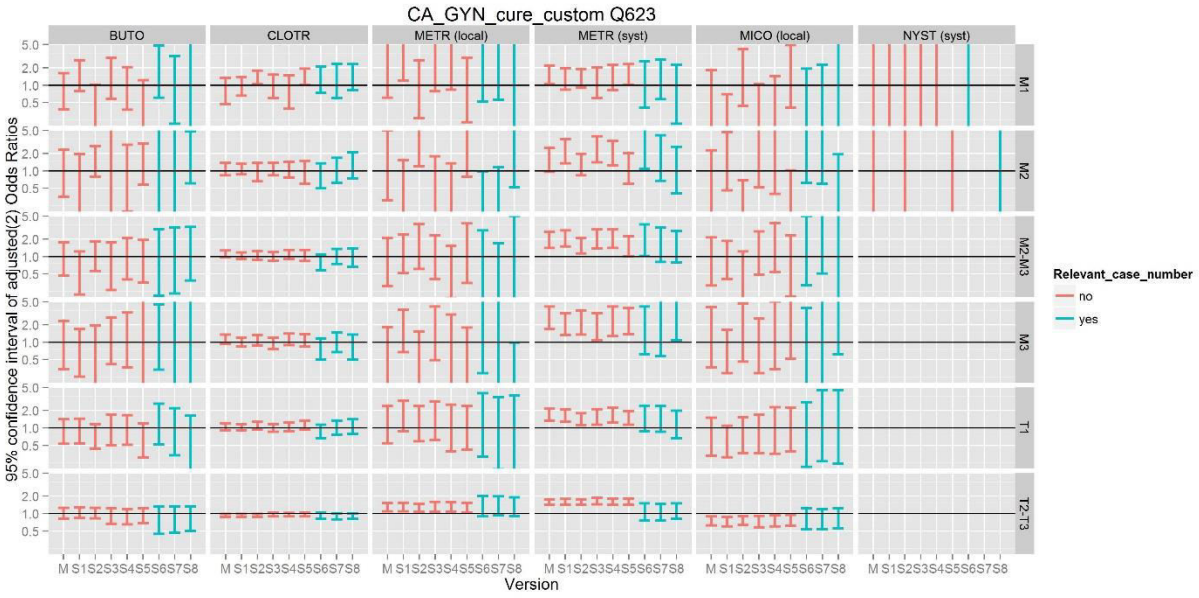
	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	2890	5.86 *
Excluding single outpatient reports (S3-S5)	1791	3.63 *
Excluding all outpatient reports (S6-S8)	793	1.61 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		0.32 **

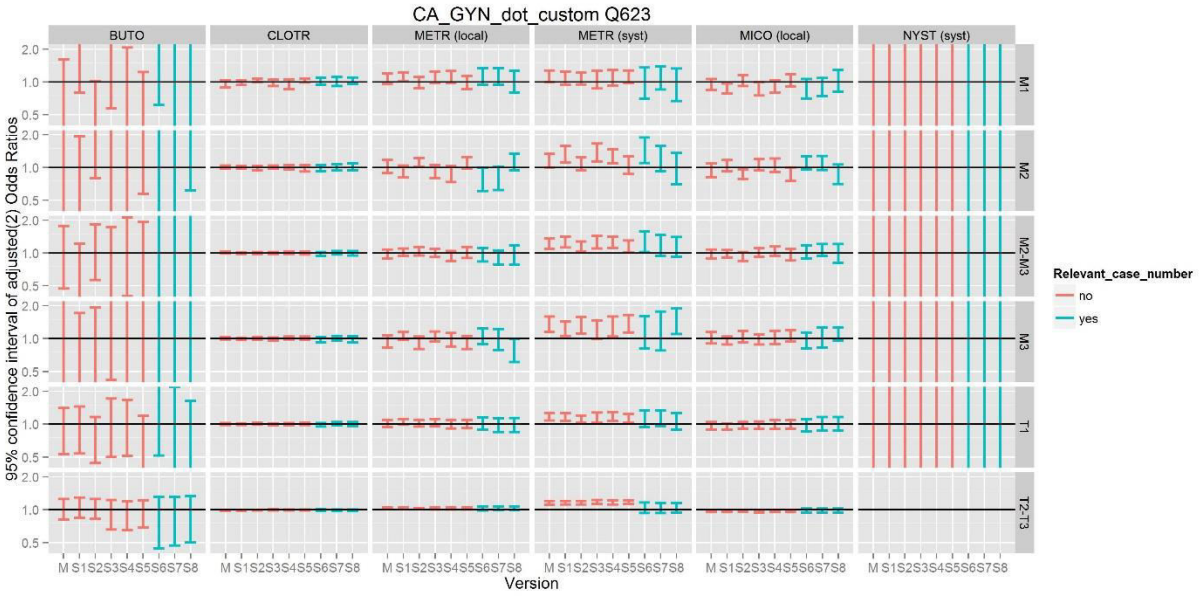
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

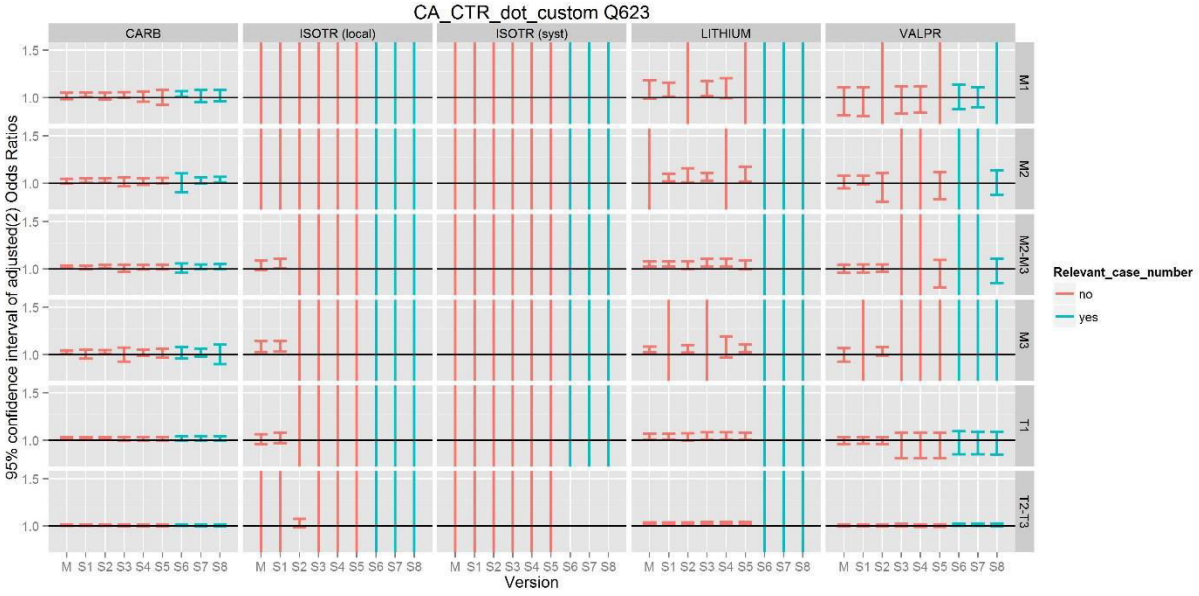
Based on the above numbers, outpatient reports may be unreliable for the analysis of this anomaly category; hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group. Note the substantial over-reporting of cases to the OEP database – due to the unspecific meaning of this code, part of the OEP reported cases may not represent severe/true congenital anomalies.

Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.S. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.S. 95% confidence intervals of odds ratios of drug exposure in the Q623 congenital anomaly group, adjusted to all confounders.
Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_custom Q623
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes


CA_CTR_dot_custom Q623
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes

15.3.21. Congenital malformation of urinary system, unspecified (Custom Q649)

The custom Q649 code group has been defined as any reported ICD code in the Q649 range.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	3101	6.28 *
Excluding single outpatient reports (S3-S5)	2419	4.90 *
Excluding all outpatient reports (S6-S8)	2041	4.14 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		0.22 **

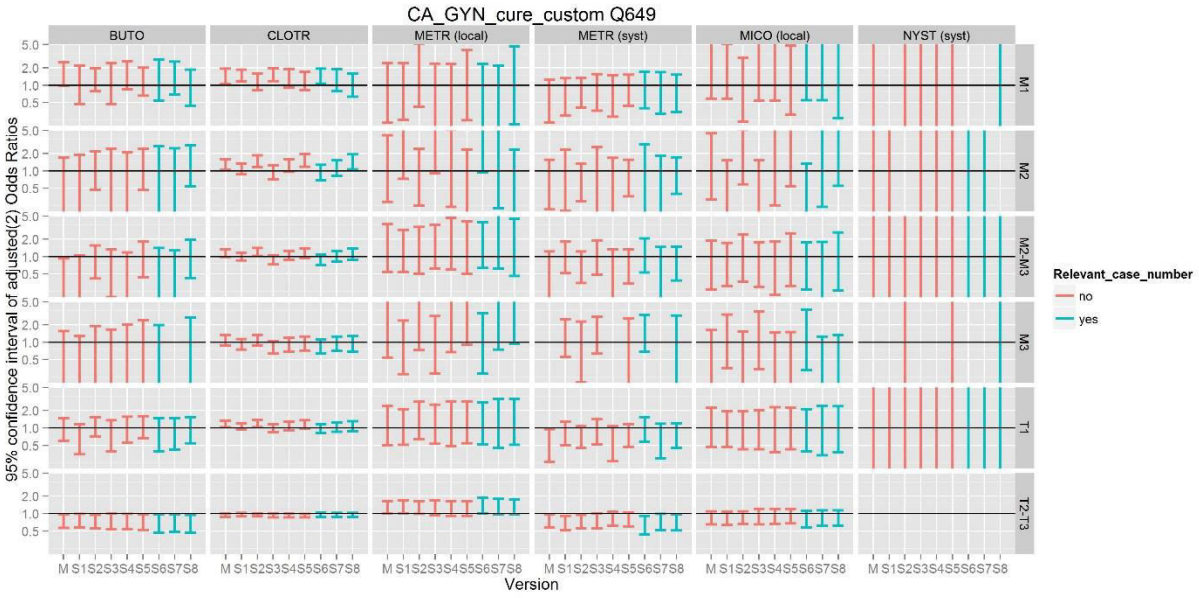
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

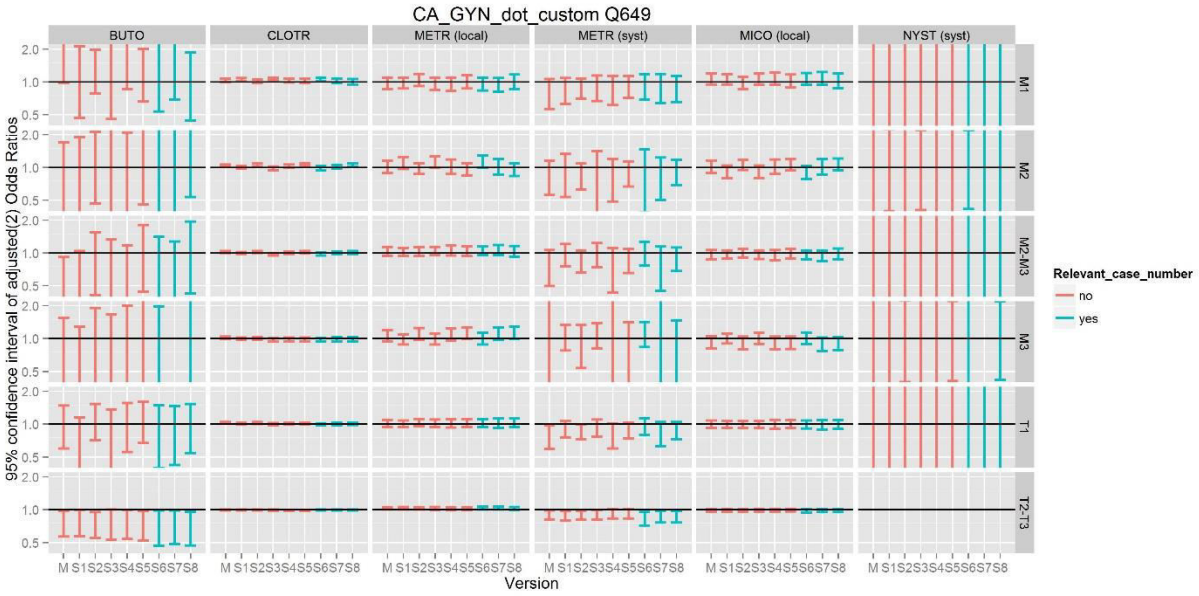
Based on the above numbers, single outpatient reports may be unreliable for the analysis of this anomaly category. Hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group. Note the substantial over-reporting of cases to the OEP database – due to the unspecific meaning of this code, part of the OEP reported cases may not represent severe/true congenital anomalies.

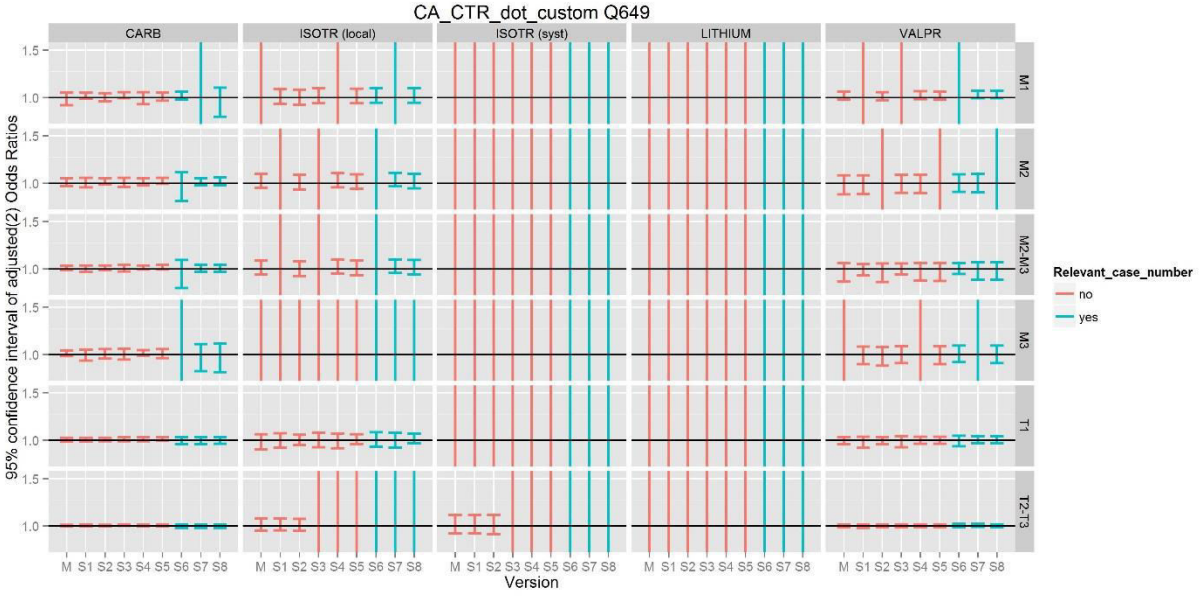
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.T. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.T. 95% confidence intervals of odds ratios of drug exposure in the Q649 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_custom Q649
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes


CA_CTR_dot_custom Q649
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes

15.3.22. Other specified congenital malformations of kidney (Custom Q638)

The custom Q638 code group has been defined as any reported ICD code in the Q638 range.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	2801	5.68 *
Excluding single outpatient reports (S3-S5)	1323	2.68 *
Excluding all outpatient reports (S6-S8)	1065	2.16 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		0.51 **

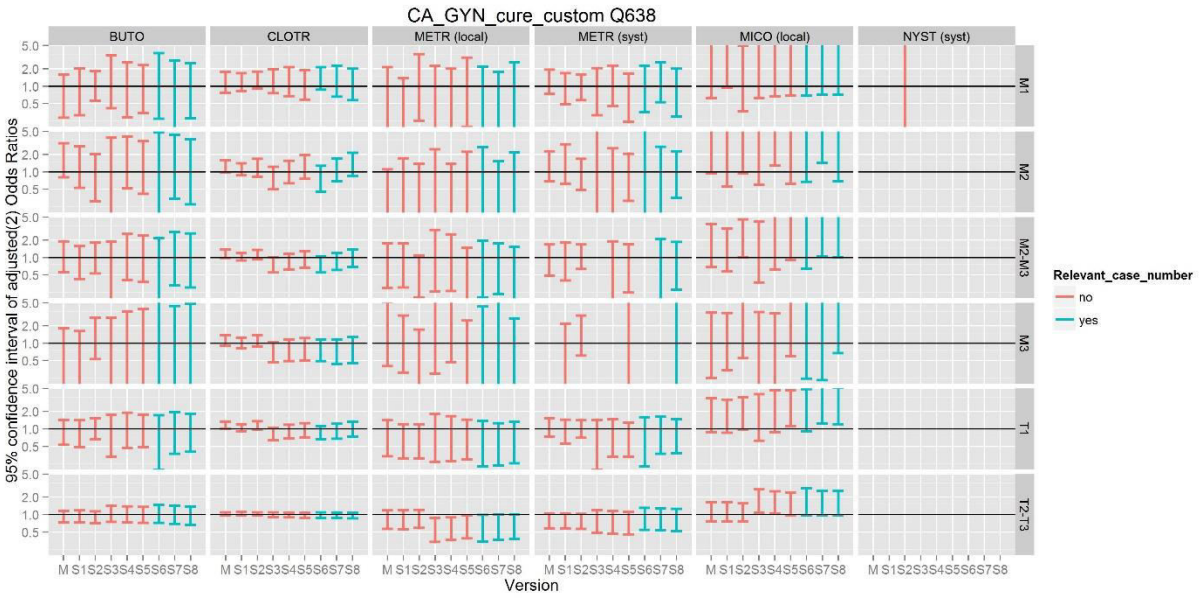
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

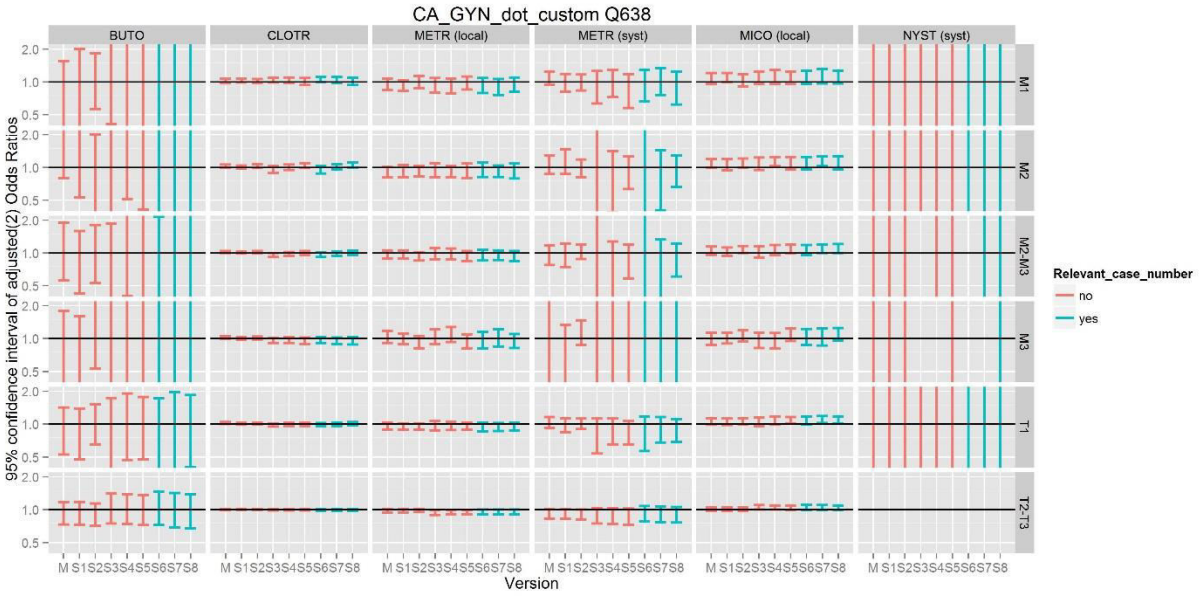
Based on the above numbers, single outpatient reports may be unreliable for the analysis of this anomaly category. Hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group. Note the substantial over-reporting of cases to the OEP database – due to the unspecific meaning of this code, part of the OEP reported cases may not represent severe/true congenital anomalies.

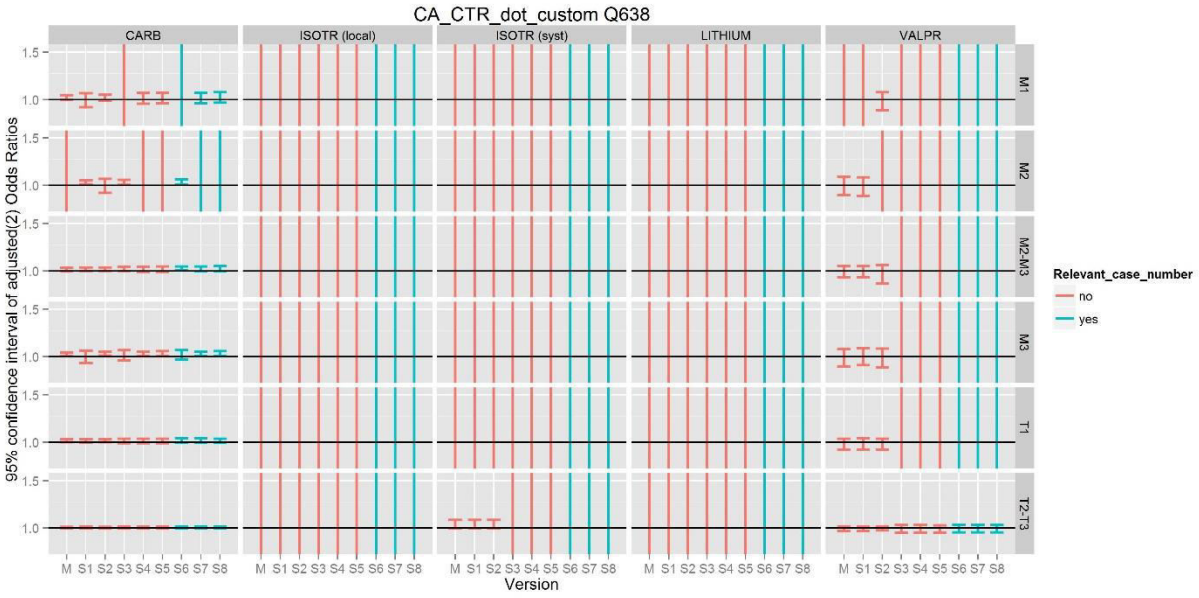
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.U. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.U. 95% confidence intervals of odds ratios of drug exposure in the Q638 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_custom Q638
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1S2S3S4S5S6S7S8
Version
Relevant_case_number
no
yes


CA_CTR_dot_custom Q638
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes

15.3.23. Congenital occlusion of ureter (Custom Q621)

The custom Q621 code group has been defined as any reported ICD code in the Q621 range.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	929	1.88 *
Excluding single outpatient reports (S3-S5)	199	0.40 *
Excluding all outpatient reports (S6-S8)	164	0.33 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		0.07 **

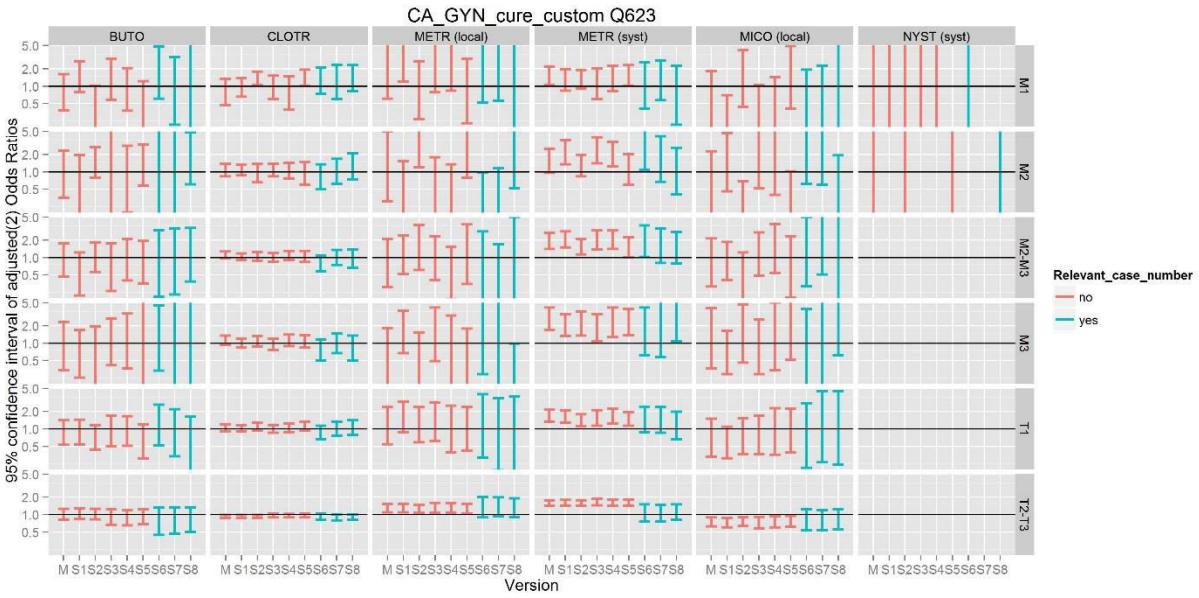
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

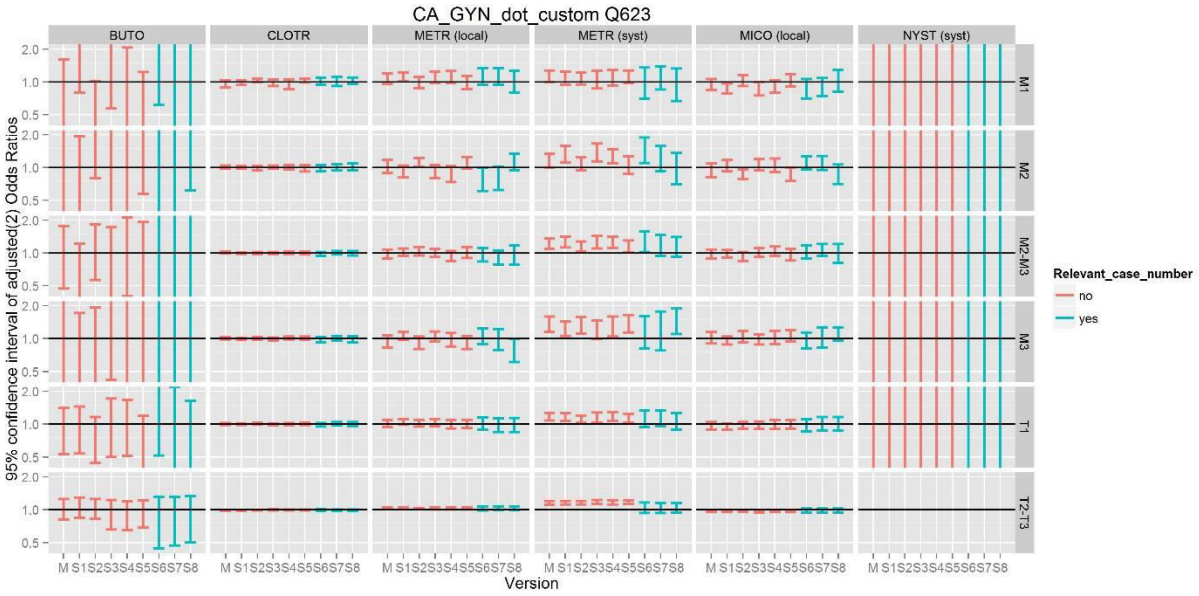
Based on the above numbers, single outpatient reports may be unreliable for the analysis of this anomaly. Hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group. The under-reporting of inpatient cases to the national registry is substantial.

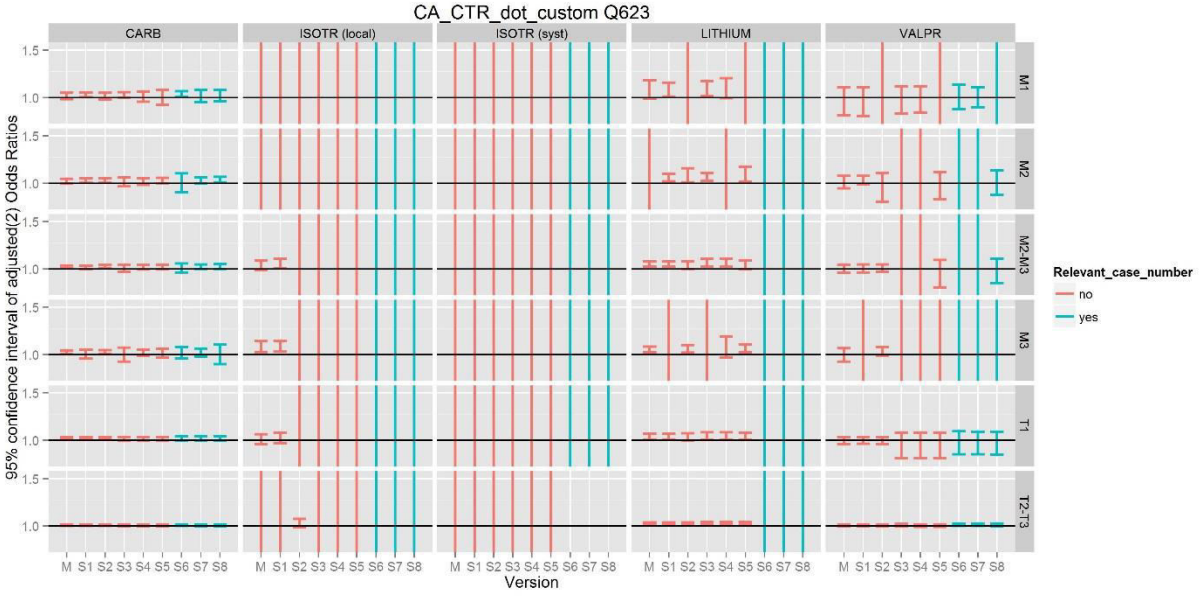
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.V. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.V. 95% confidence intervals of odds ratios of drug exposure in the Q621 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_custom Q623
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes


CA_CTR_dot_custom Q623
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes

15.3.24. Urinary, other (Custom RG10)

The custom RG10 code group has been defined as any reported al52 code except for Q620, Q639, Q623, Q649, Q638, Q621.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	2507	5.08 *
Excluding single outpatient reports (S3-S5)	1381	2.80 *
Excluding all outpatient reports (S6-S8)	1090	2.21 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		1.04 **

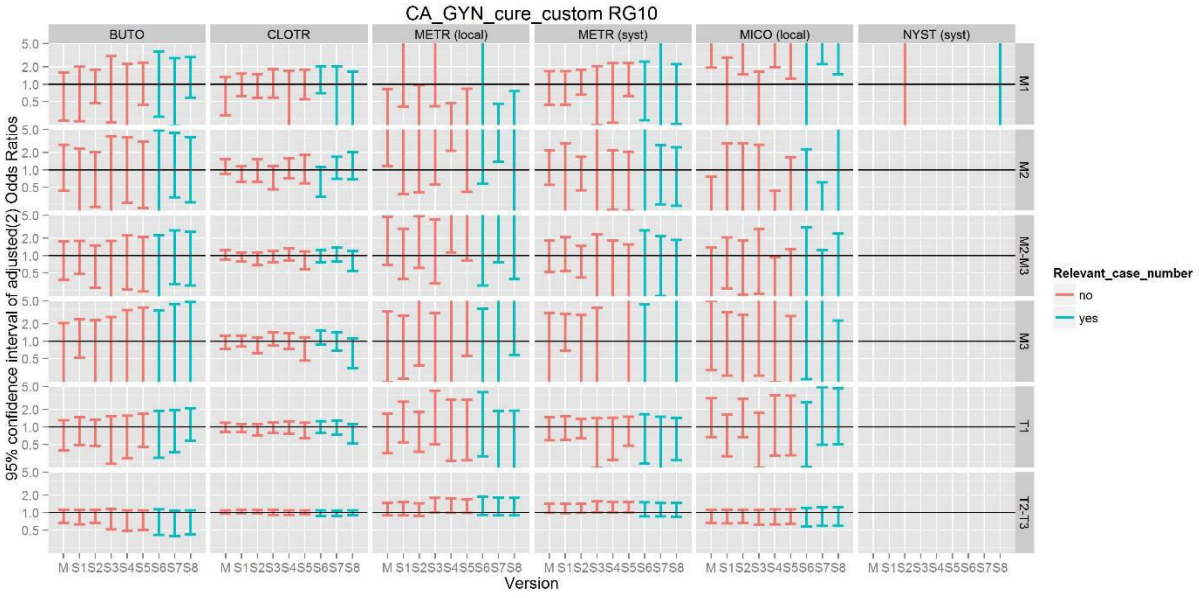
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

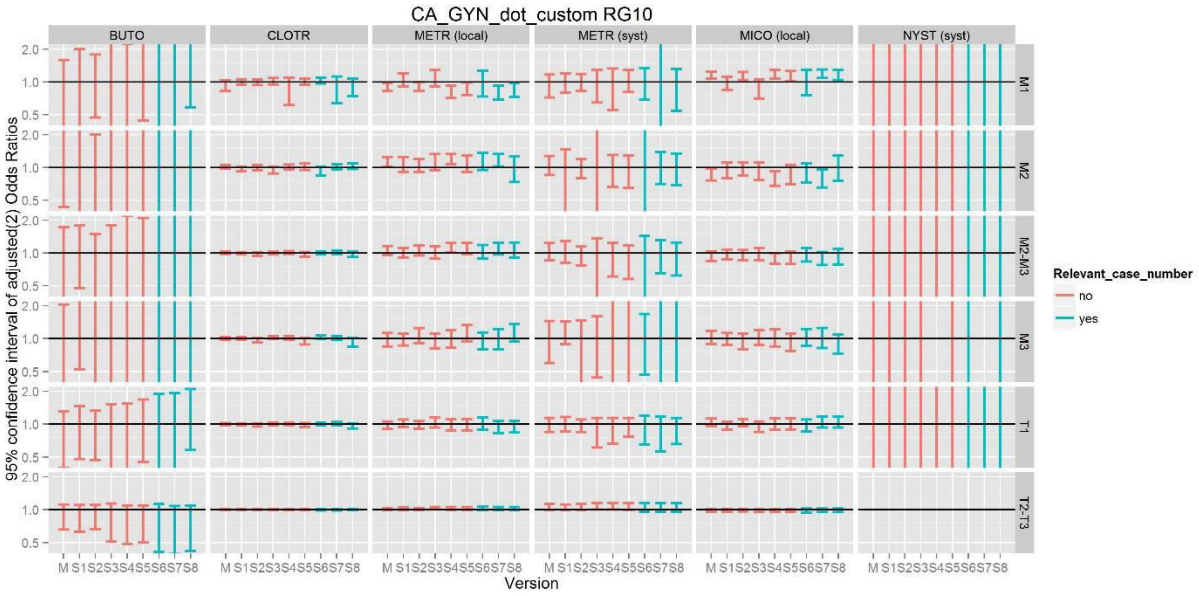
Based on the above numbers, single outpatient reports may be unreliable for the analysis of this anomaly category. Hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group.

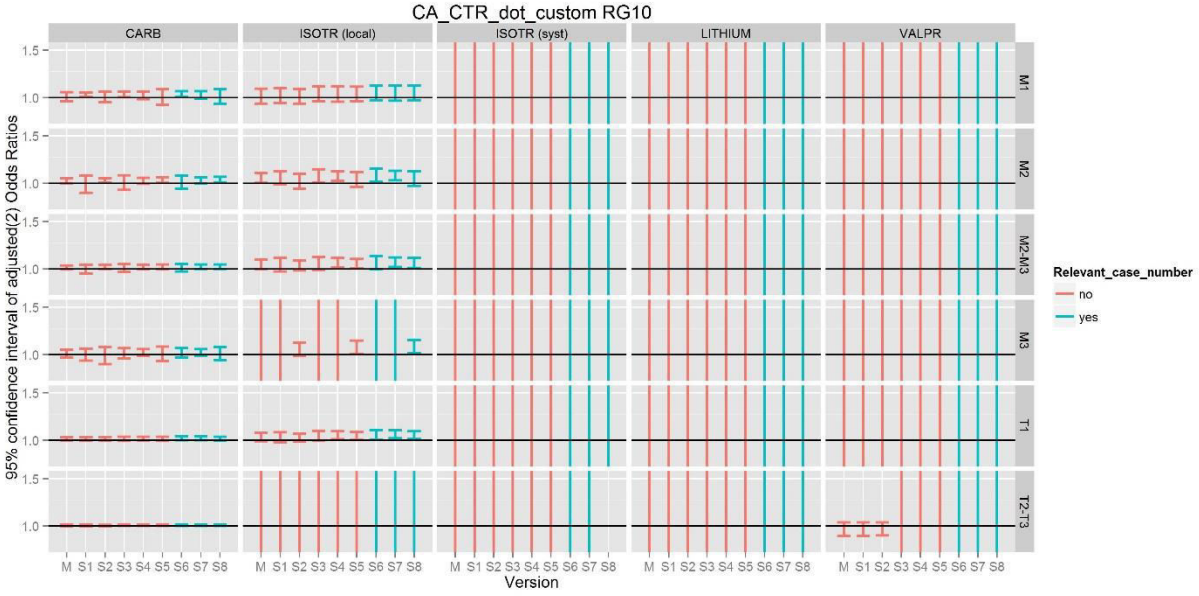
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.W. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.W. 95% confidence intervals of odds ratios of drug exposure in the RG10 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_custom RG10
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
M S1 S2 S3 S4 S5 S6 S7 S8
Relevant_case_number
no
yes


CA_CTR_dot_custom RG10
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
M S1 S2 S3 S4 S5 S6 S7 S8
Relevant_case_number
no
yes

15.3.25. Genital (EUROCAT al58)

The EUROCAT al58 code group has been defined as any reported ICD code in the Q50-Q52 and Q54-Q56 ranges.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	3062	6.20 *
Excluding single outpatient reports (S3-S5)	1687	3.42 *
Excluding all outpatient reports (S6-S8)	1514	3.07 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		2.15 **

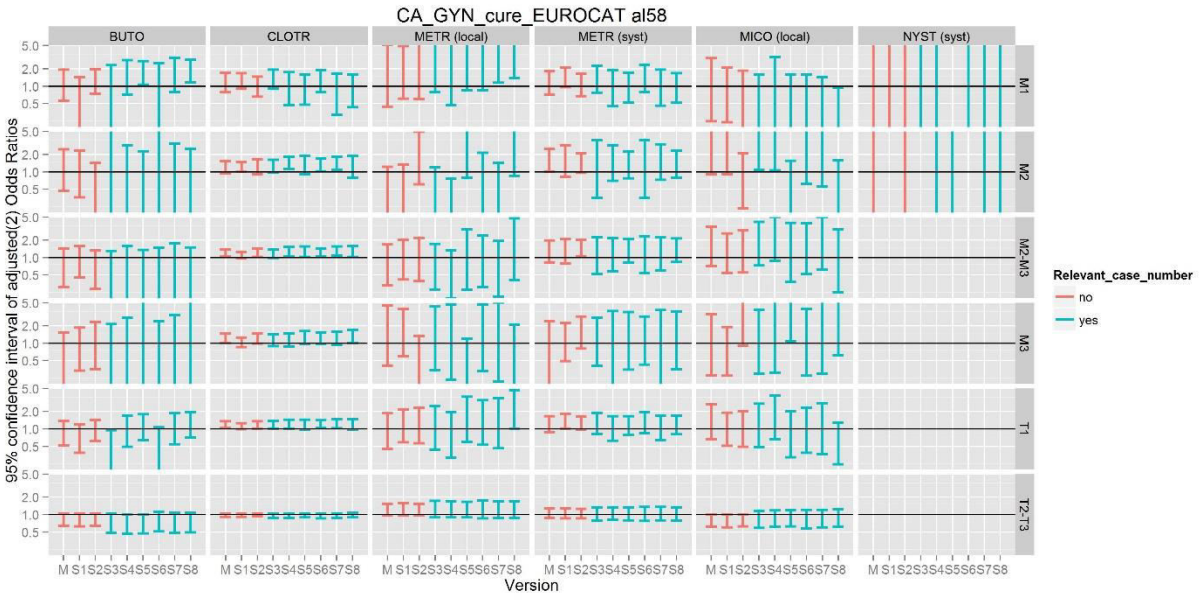
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

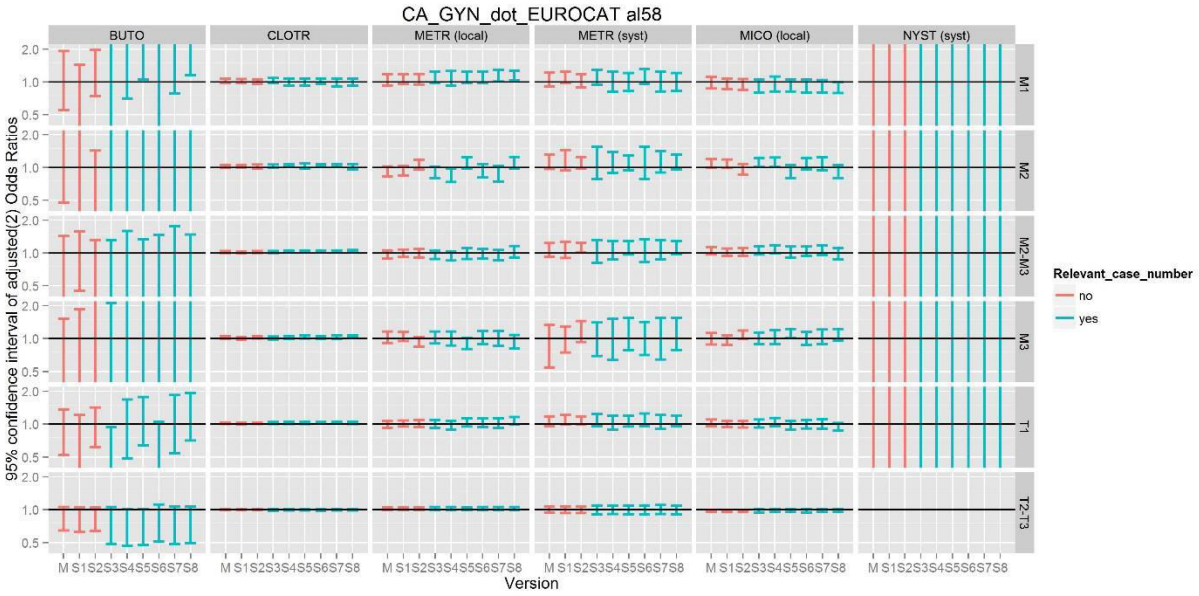
Based on the above numbers, single outpatient reports may be unreliable for the analysis of genital anomalies; hence, sensitivity analyses S3-S8 are the most relevant ones for the analysis of this code group.

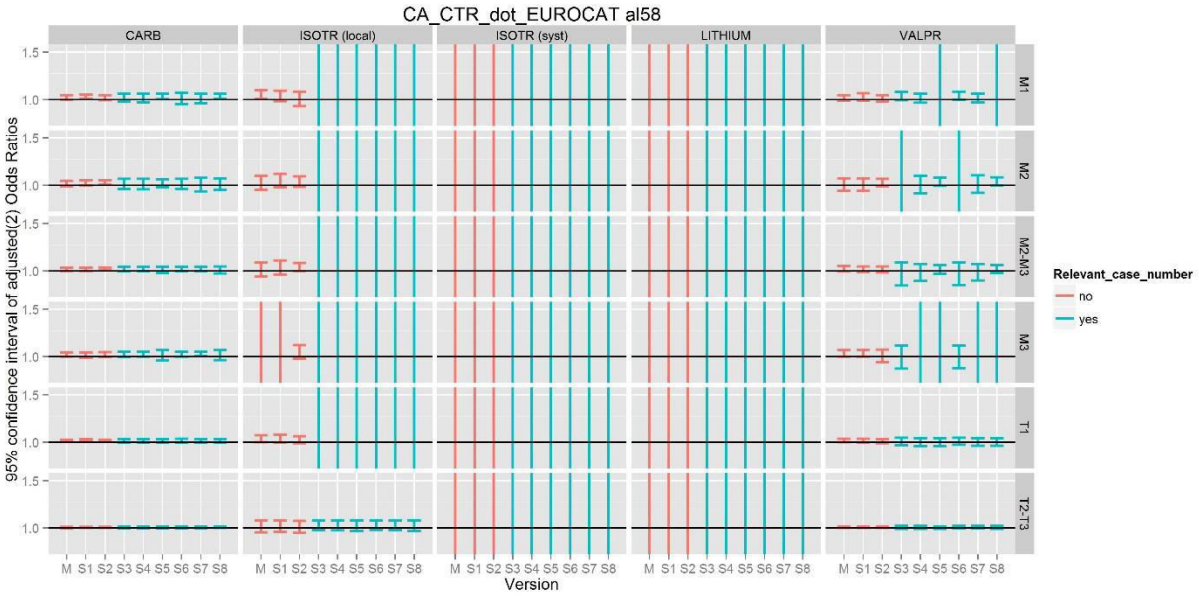
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.X. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.X. 95% confidence intervals of odds ratios of drug exposure in the al58 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al58
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1S2S3S4S5S6S7S8
Version
Relevant_case_number
no
yes


CA_CTR_dot_EUROCAT al58
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes

15.3.26. Hypospadia (EUROCAT al59)

The EUROCAT al59 code group has been defined as any reported ICD code in the Q54 range.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	1932	3.91 *
Excluding single outpatient reports (S3-S5)	1184	2.40 *
Excluding all outpatient reports (S6-S8)	1100	2.23 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		1.83 **

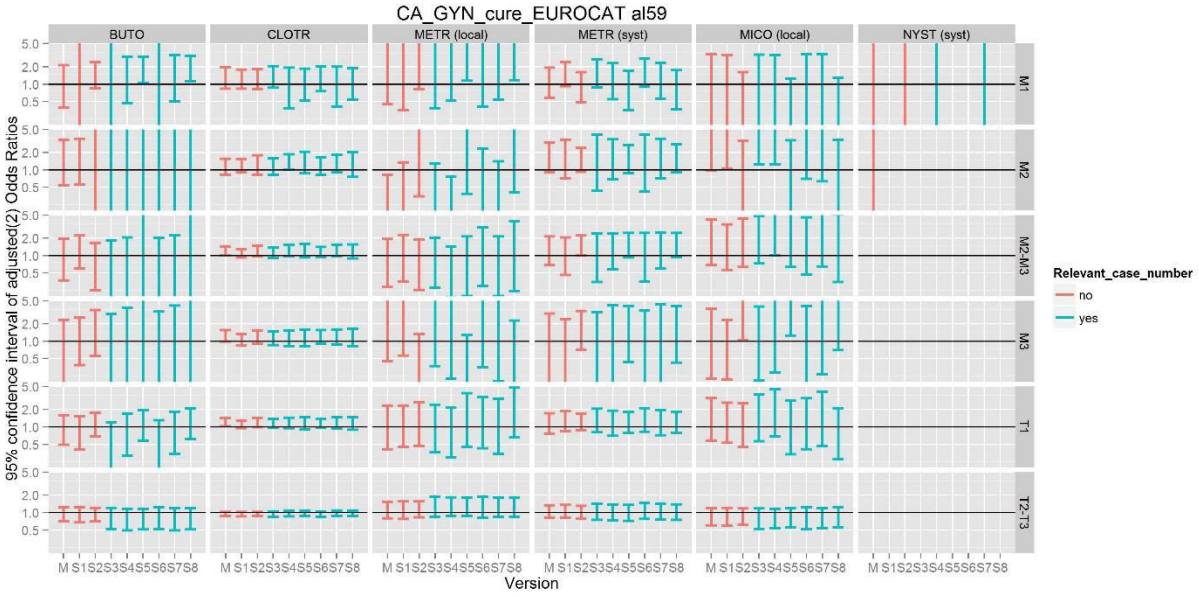
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

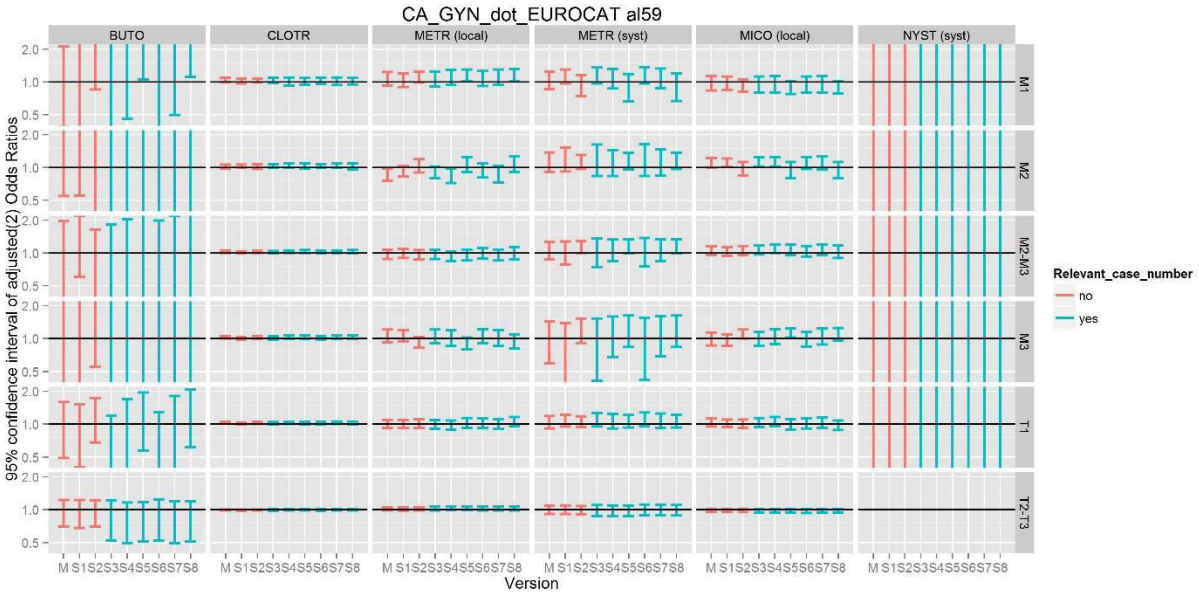
Based on the above numbers, single outpatient reports may be unreliable for the analysis of genital anomalies; hence, sensitivity analyses S3-S8 are the most relevant ones for the analysis of this code group.

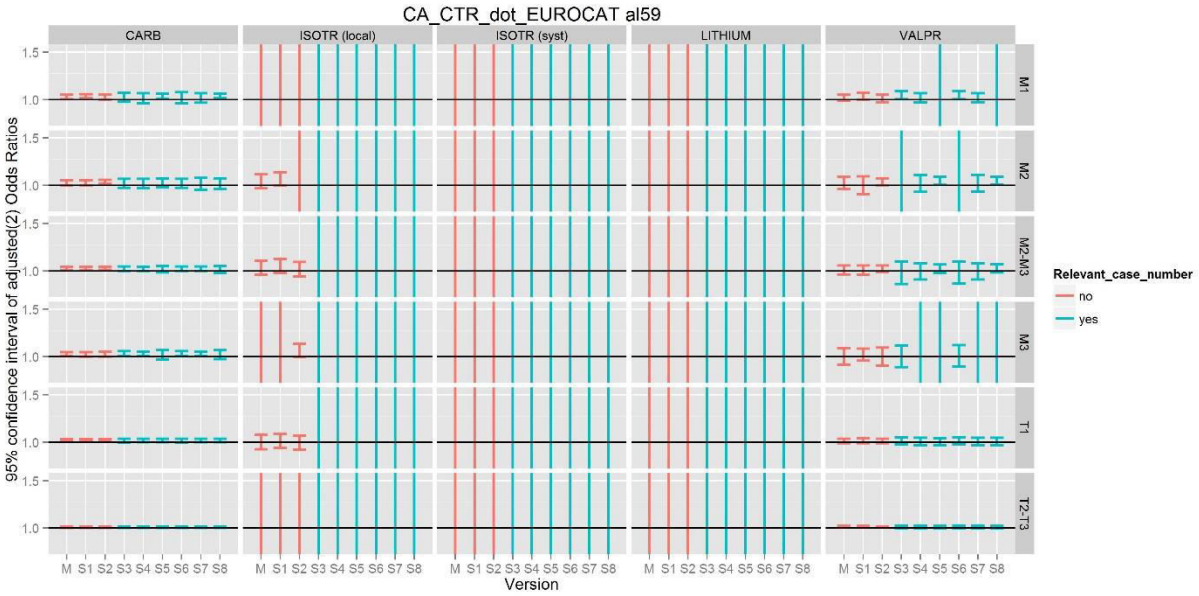
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.Y. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.Y. 95% confidence intervals of odds ratios of drug exposure in the al59 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al59
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes


CA_CTR_dot_EUROCAT al59
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes