

# Oesophageal atresia: prevalence, prenatal diagnosis and associated anomalies in 23 European regions

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## ABSTRACT

**Objective** To describe prevalence, prenatal diagnosis and epidemiological data on oesophageal atresia from 23 well-defined European regions and compare the prevalence between these regions.

**Design** Population-based study using data from a large European database for surveillance of congenital anomalies (EUROCAT) for two decades (1987–2006).

**Settings** Twenty-three participating registries based on multiple sources of information including information about live births, fetal deaths with gestational age  $\geq 20$  weeks and terminations of pregnancy.

**Patients** 1222 cases of oesophageal atresia in a population of 5 019 804 births.

**Results** The overall prevalence was 2.43 cases per 10 000 births (95% CI 2.30 to 2.57). There were regional differences in prevalence ranging from 1.27 to 4.55. Prenatal detection rates varied by registry from  $>50\%$  of cases to  $<10\%$  of cases. A total of 546 cases (44.7%) had an isolated oesophageal anomaly, 386 (31.6%) were multiple malformed and 290 (23.7%) had an association or a syndrome. There were 1084 live born cases (88.7%), 43 cases were fetal deaths and 95 cases were terminations of pregnancy. One-week survival for live births was 86.9% and 99.2% if the gestational age was  $\geq 38$  weeks and isolated oesophageal atresia was present. Males accounted for 57.3% of all cases and 38.5% of live born cases were born with gestational age  $<37$  weeks.

**Conclusion** There were regional differences in prevalence of oesophageal atresia in Europe. Half of all cases had associated anomalies. Prenatal detection rate increased from 26% to 36.5% over the two decades. Survival in infants with isolated oesophageal atresia born at term is high.

## INTRODUCTION

Oesophageal atresia is a congenital anomaly of the oesophagus and in most cases involves the trachea. The prevalence in reported case series varies from 1 in 2500 to 1 in 4500 births.<sup>1–5</sup> The anomaly arises from a developmental disruption with faulty separation of the embryogenic foregut into trachea and oesophagus during the fifth to sixth week of embryonic life. In 78–90% of reported cases there is a tracheo-oesophageal fistula between the lower segment of the oesophagus and trachea (gross type C).<sup>5–14</sup> The aetiology of oesophageal atresia is unknown. Different environmental factors have been suggested to play a role in the development of oesophageal atresia.<sup>15</sup>

## What is already known on this topic

- ▶ The prognosis after surgery is good in term infants with isolated oesophageal atresia.
- ▶ Prevalence varies in different populations and no changes in prevalence over time have been shown.
- ▶ The proportion of associated anomalies is high.

## What this study adds

- ▶ Prevalence of oesophageal atresia has been stable over the last 20 years. The prevalence differs within European regions.
- ▶ The study characterises the associated anomalies and documents their impact on mortality in patients with oesophageal atresia.
- ▶ Prenatal detection rates of oesophageal atresia are increasing; termination of pregnancy for isolated oesophageal atresia is very rare.

Associated anomalies are reported to be present in a high proportion of patients with oesophageal atresia.<sup>1 3–6 13 14 16–22</sup> Associated anomalies can be chromosomal (Down's syndrome, Edward's syndrome (trisomy 18)), part of a genetic syndrome (CHARGE syndrome, Feingold syndrome and others), an association such as VACTERL-association or multiple anomalies without a pattern.

Survival with oesophageal atresia is only possible with surgical correction. Survival rates after surgery are reported to be around 90% including patients with severe associated anomalies and up to almost 100% in term infants without associated anomalies.<sup>17 20 23–25</sup> Some studies only include cases referred for surgery and not the total population of live born cases with oesophageal atresia.

The aim of this study was to present data on prevalence, clinical characteristics and prenatal diagnosis of oesophageal atresia in Europe using a large European database of congenital anomalies (EUROCAT).

## METHODS

The study is based on routinely collected data from 23 European registries of congenital anomalies (EUROCAT). The registries are population-based and cover geographically well-defined populations including all births from mothers residing in the

**Table 1** Number of cases, prevalence, number of cases with prenatal diagnosis and prenatal detection rate by registry

Registry	Country	Years included	Total births	Total cases	Total prevalence* (95% CI)	Cases with prenatal diagnosis	% Prenatal diagnosis (95% CI)
Mainz	Germany	1990–2006	59403	27	4.55 (3.13 to 6.61)	14	51.9 (33.9 to 69.4)
Odense	Denmark	1987–2006	110788	47	4.24 (3.1 to 5.64)	6	12.8 (6.1 to 25.2)
Emilia Romagna	Italy	1987–2006	540233	186	3.44 (2.97 to 3.96)	50	26.9 (21.0 to 33.9)
Strasbourg	France	1987–2004	231322	75	3.24 (2.59 to 4.06)	27	36.0 (26.1 to 47.3)
Northern Region	UK	2000–2006	214037	65	3.04 (2.38 to 3.87)	35	53.8 (41.8 to 65.4)
Vaud	Switzerland	1989–2006	134746	39	2.89 (2.12 to 3.96)	12	30.8 (18.6 to 46.5)
Styria	Austria	1987–2005	228231	61	2.67 (2.08–3.43)		
Wales	UK	1998–2006	288877	76	2.63 (2.10–3.29)	32	42.1 (31.6 to 53.4)
The Netherlands	Netherlands	1987–2006	375050	94	2.51 (2.10 to 3.10)	25	26.6 (18.7 to 36.4)
Isle de Reunion	France	2002–2006	73023	17	2.33 (1.46 to 3.73)	10	58.8 (35.7 to 78.5)
Wessex	UK	1994–2006	341119	79	2.32 (1.86 to 2.89)	37	46.8 (36.2 to 57.8)
Saxony Anhalt	Germany	2000–2006	123241	28	2.27 (1.58 to 3.28)		
Antwerp	Belgium	1993–2006	222265	50	2.25 (1.71 to 2.97)		
Ukraine	Ukraine	2005–2006	54193	11	2.03 (1.14 to 3.63)	6	54.5 (27.7 to 78.9)
Trent	UK	1998–2006	549515	108	1.97 (1.63 to 2.37)		
Dublin	Ireland	1987–2006	412564	81	1.96 (1.58 to 2.44)		
Malta	Malta	1991–2006	71754	14	1.95 (1.17 to 3.27)	1	7.1 (1.7 to 31.9)
Tuscany	Italy	1988–2006	430462	80	1.86 (1.49 to 2.31)	12	15.0 (8.8 to 24.4)
Barcelona	Spain	1993–2006	182683	30	1.64 (1.15 to 2.34)	15	50.0 (33.1 to 66.9)
Thames Valley	UK	1991–2006	140203	23	1.64 (1.10 to 2.46)	7	30.4 (15.6 to 51.1)
Cork and Kerry	Ireland	1997–2003	55630	8	1.44 (0.74 to 2.83)	3	37.5 (13.7 to 70.1)
South East Ireland	Ireland	1997–2005	54837	7	1.28 (0.63 to 2.63)		
Zagreb	Croatia	1987–2006	125628	16	1.27 (0.79 to 2.07)	1	6.3 (1.5 to 28.7)
Total		1987–2006	5019804	1222	2.43 (2.30 to 2.57)	293 of 887	33.0 (30.0 to 36.2)

The prevalence of oesophageal atresia in the 23 regions ranged from 1.27 per 10 000 births in Zagreb and 1.28 per 10 000 births in South East Ireland to 4.24 per 10 000 births in Odense and 4.55 per 10 000 births in Mainz.

\*Rate per 10 000.

registry area. For further details on population coverage and registration methods see <http://www.euocat-network.eu>.<sup>26</sup> The registries are all based on multiple sources of information including hospital records, birth and death certificates and postmortem examinations, and include information about live births, fetal deaths with gestational age  $\geq 20$  weeks and termination of pregnancy after prenatal diagnosis of fetal anomaly (termination of pregnancy for fetal anomaly (TOPFA)). All structural anomalies, syndromes and chromosomal anomalies are included in the database except minor and poorly specified anomalies as defined by the EUROCAT exclusion list.<sup>27</sup> Only cases with diagnosis of oesophageal atresia confirmed postnatally are included in the database, except for a few prenatally diagnosed TOPFA cases where postmortem examination was not performed.

All cases with oesophageal atresia coded with relevant WHO International Classification of Diseases 9 (ICD9) code (75030, 75031) or ICD10 code (Q39.0 and Q39.1) and delivered during 1987–2006 were included in this study. Not all registries covered all years.

Data items included in the analysis are: birth outcome, year of birth, infant sex, gestational age, time of diagnosis (pre or postnatally), death within the first week after birth and information on associated anomalies, syndromes or associations.

The EUROCAT flowchart for multiple anomalies was used to find the potential multiple anomaly cases.<sup>27</sup>

These cases were manually reviewed by a paediatrician (EG) and a geneticist (EC) and classified as isolated oesophageal atresia, multiple congenital anomalies (two or more major anomalies in different organ systems), chromosomal or non-chromosomal syndrome or association. Throughout this paper isolated oesophageal atresia is defined as oesophageal atresia gross type A–D without associated anomalies.

The total number of births covered by the 23 registries over the period of study years was 5 019 804.

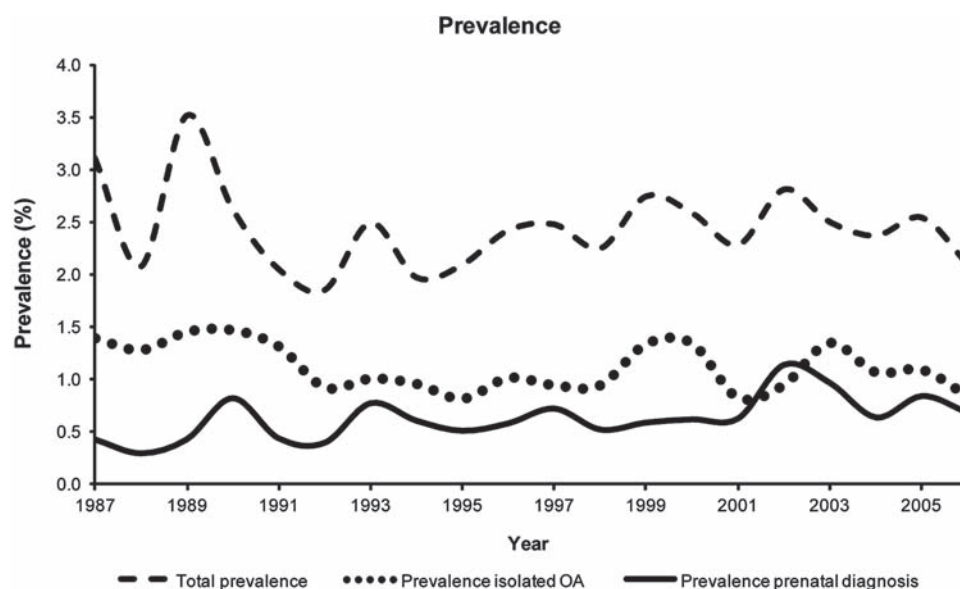
Continuous variables were presented as means and SDs and categorical variables as numbers and percentages. We used the Student *t* test to test for differences between independent continuous variables and the  $\chi^2$  test to test for differences between categorical variables. Due to a non-Gaussian distribution of gestational age, the median and IQR and a Mann–Whitney test were used to compare groups. A *p* value  $<0.05$  was considered statistically significant. STATA V.9.2 was used for the statistical analysis.

## RESULTS

During the study period 1222 cases of oesophageal atresia from the 23 registries were recorded giving a total prevalence of 2.43 per 10 000 births (95% CI 2.30 to 2.57). Large regional differences were found in both the total prevalence of all cases of oesophageal atresia and in the prevalence of isolated oesophageal atresia (table 1 and figure 1).

The overall prevalence of oesophageal atresia in the two 10 year periods (1987–1996 and 1997–2006) was 2.37 and 2.46 per 10 000 births. This difference between the two decades did not reach statistical significance. For prevalence of oesophageal atresia, isolated oesophageal atresia and prenatal diagnosis over time see figure 1.

A total of 1084 of 1222 cases (88.7%) were live births, 43 (3.5%) were fetal deaths and 95 (7.8%) cases resulted in termination of pregnancy. Among the 1222 cases there were 700 males (57.3%) and 517 females (42.3%) giving a male:female ratio of 1:0.74. In four cases the sex was indeterminable and in one case sex was not recorded in the registry. A breakdown of infant sex and birth type for all subgroups is provided in table 2.



**Figure 1** Total prevalence, prevalence of isolated oesophageal atresia (OA) and prevalence of prenatal diagnosis per year.

**Table 2** Classification of oesophageal atresia cases, infant sex distribution and birth outcome

Specified	Number	Percentage	Sex	Number	Percentage	Birth type	Number	Percentage
Isolated oesophageal atresia	546	44.7	Male	310	56.8	LB	535	98.0
			Female	234	42.9	SB	8	1.5
			I/NK	2	0.4	TOPFA	3	0.5
VACTERL association	117	9.6	Male	68	58.1	LB	94	80.3
			Female	48	41.0	SB	3	2.6
			I/NK	1	0.9	TOPFA	20	17.1
CHARGE syndrome	12	1.0	Male	6	50.0	LB	12	100.0
			Female	6	50.0	SB	0	0.0
						TOPFA	0	0.0
Other non-chromosomal syndrome	56	4.6	Male	34	60.7	LB	49	87.5
			Female	22	39.3	SB	2	3.6
						TOPFA	5	8.9
Down's syndrome	23	1.9	Male	14	60.9	LB	17	73.9
			Female	9	39.1	SB	1	4.3
						TOPFA	5	21.7
Edward's syndrome	72	5.9	Male	31	43.1	LB	29	40.3
			Female	41	56.9	SB	15	20.8
						TOPFA	28	38.9
Other chromosomal syndrome	10	0.8	Male	6	60.0	LB	7	70.0
			Female	4	40.0	SB	0	0.0
						TOPFA	3	30.0
Multiple malformed	386	31.6	Male	231	59.8	LB	341	88.3
			Female	153	39.6	SB	14	3.6
			I/NK	2	0.5	TOPFA	31	8.0
Total	1222	100.0	Male	700	57.3	LB	1084	88.7
			Female	517	42.3	SB	43	3.5
			I/NK	5	0.4	TOPFA	95	7.8

I/NK, indeterminate/not known; LB, live birth; SB, stillbirth; TOPFA, termination of pregnancy for fetal anomaly.

### Associated anomalies

The 1222 cases were classified in three groups: 546 (44.7%) had an isolated oesophageal atresia, 386 (31.6%) had multiple anomalies, 290 (23.7%) had an association or syndrome (table 2). Syndromic cases or those with associated anomalies were subdivided in the following six groups: 117 (9.6%) had

VACTERL association, 12 cases (1.0%) CHARGE syndrome, 56 cases (4.6%) had another non-chromosomal syndrome, 23 cases (1.9%) Down's syndrome, 72 cases (5.9%) Edward's syndrome and 10 cases (0.8%) another chromosomal syndrome. The most common associated anomalies among the 1222 cases were other gastrointestinal anomalies, congenital heart

**Table 3** One-week survival and frequency of trachea-oesophageal fistula (TF) for all live born cases with oesophageal atresia given per subgroup

Specified	Number of live births	Survival beyond 1 week	Number	Percentage	TF*	Number*	Percentage*
Isolated oesophageal atresia	438	Yes	407	92.9	Yes	281	69.0
		No	15	3.4	No	126	31.0
		NK	16	3.7			
VACTERL association	89	Yes	77	86.5	Yes	65	84.4
		No	11	12.4	No	12	15.6
		NK	1	1.1			
CHARGE syndrome	7	Yes	5	71.4	Yes	4	80.0
		No	2	28.6	No	1	20.0
		NK	0				
Other non-chromosomal syndrome	45	Yes	36	80.0	Yes	32	88.9
		No	9	20.0	No	4	11.1
		NK	0				
Down's syndrome	15	Yes	12	80.0	Yes	4	33.3
		No	3	20.0	No	8	67.7
		NK	0				
Edward's syndrome	26	Yes	3	11.5	Yes	2	67.7
		No	22	84.6	No	1	33.3
		NK	1	3.8			
Other chromosomal syndrome	6	Yes	5	83.3	Yes	4	80.0
		No	1	16.7	No	1	20.0
		NK	0				
Multiple malformed	299	Yes	259	86.6	Yes	189	73.0
		No	34	11.4	No	70	27.0
		NK	6	2.0			
Total	925	Yes	804	86.9	Yes	581	72.2
		No	97	10.5	No	224	27.8
		NK	24	2.6			

\*Data on TF only on live born cases surviving more than 1 week.  
NK, not known.

defects, and limb and urinary tract anomalies. Associated congenital heart defects was diagnosed in 359 of cases (29.4%), urinary tract anomalies in 200 cases (16.4%), other gastrointestinal anomalies in 190 cases (15.5%) and limb anomalies in 160 cases (13.1%). The most common congenital heart defects associated with oesophageal atresia were tetralogy of fallot, atrial septal defect, ventricular septal defect and transposition of the great arteries.

### Tracheo-oesophageal fistula

Based on the WHO ICD9 and ICD10 codes provided by the registries, 581 of the 925 live born cases (72.2%) had an associated tracheo-oesophageal fistula. The frequency of tracheo-oesophageal fistula in cases with isolated oesophageal atresia was 69.0% and 75.4% for cases with associated anomalies (table 3).

### Time of diagnosis

Prenatal detection rates showed large regional differences with rates between 50% and 65% in Barcelona, Mainz, Ukraine, Thames Valley, Isle de Reunion and Northern Region, UK but <10% in Zagreb and Malta. Over the two decades 1987–1996 and 1997–2006 there was a statistically significant increase in prenatal detection rates (26.0% and 36.5% respectively,  $\chi^2=9.65$ ,  $p<0.01$ ).

For 96.5% ( $n=693$ ) of the live born cases with a postnatal diagnosis, the time of diagnosis was known: 83.4% of these cases were detected at birth, 15.4% within the first week of life and 1.2% of cases after the first week of life.

### Gestational age

Gestational age at birth was less than 37 weeks for 401 of the 1042 (38.5%) live born infants with data on gestational age. For live born infants with isolated oesophageal atresia 32.3% were born preterm and for live born infants with associated anomalies 40.6% were born preterm. For live born infants diagnosed postnatally with isolated oesophageal atresia 32.4% were born preterm.

### Termination of pregnancy

Of the 351 prenatally diagnosed cases termination of pregnancy was performed in 95 cases (27.1%). Median gestational age at prenatal diagnosis was 20 weeks (18–23 weeks) and 34 cases were diagnosed before gestational age 20 weeks. There were 20 TOPFA cases with VACTERL, 28 with Edward's syndrome, 31 were multiple malformed and only three TOPFA cases had isolated oesophageal atresia (table 2).

### Survival

Data on 1-week survival was available from 19 registries (four registries were excluded as data on 1-week survival was missing for >10% of cases). One-week survival for all live births was 86.9% ranging from 92.9% for cases with isolated oesophageal atresia to 11.5% for cases with Edward syndrome (table 3). In 11 registry areas 1-week survival for isolated oesophageal atresia was 100% and lowest regional 1-week survival was 87.5% with isolated oesophageal atresia. One-week survival rate in live born cases with isolated oesophageal atresia, gestational age  $\geq 38$  weeks and data on survival was 99.2%.



## DISCUSSION

This population-based case series describes in a standardised way a large number of cases with oesophageal atresia showing a total prevalence of 2.43 cases per 10 000 births. No differences in the prevalence over time were observed in this study, in accord with the EUROCAT statistical monitoring report for 2007 that did not show any pan-European increase in the incidence for oesophageal atresia for the years 1998–2007.<sup>28</sup>

Large variations in prevalence were found within this European population suggesting that there is a real difference in prevalence of oesophageal atresia across Europe as the registries all followed a standardised methodology. It is known for other congenital anomalies such as facial clefts, neural tube defects and omphalocele that there are regional European differences in prevalence.<sup>29–31</sup> However, there may be some under ascertainment of oesophageal atresia cases in the registries with the lowest prevalence. There was no obvious pattern in the differences of prevalence in terms of a north–south or east–west gradient. We found large regional differences in both the prevalence of all cases and in cases with isolated oesophageal atresia. In registries with prevalence below 2 per 10 000 births the fraction of non-isolated cases was lower than that in the other registries. This finding might be due to under diagnosis of oesophageal atresia in cases with multiple anomalies and syndromic cases dying before the oesophageal atresia is recognised.

Depaepe *et al*<sup>1</sup> analysed 442 cases of oesophageal atresia including cases with isolated tracheo-oesophageal fistula born during 1980–1988 and found an overall prevalence of 2.86 per 10 000 births, a significantly higher prevalence ( $p < 0.01$ ) compared with the total prevalence in the present study. This difference may be explained by their inclusion of cases with isolated tracheo-oesophageal fistula.

We found a high proportion of associated anomalies with only 44.7% of all cases with an isolated oesophageal atresia. This high proportion of associated anomalies has been reported by others.<sup>1 3–6 13 14 16–22</sup> Although most other major congenital anomalies are reported with a percentage of isolated cases up to 90%, cases with hydrocephalus and omphalocele also make up this high proportion of associated anomalies as for oesophageal atresia.<sup>29 30 32 33</sup> It is important to evaluate the fetus for associated anomalies as these can be of prognostic and therapeutic importance for the baby at birth or later in infancy.

In the present report a tracheo-oesophageal fistula was found in 72.2 % of cases, 69.0% of cases with isolated oesophageal atresia and 75.4% of cases with non-isolated oesophageal atresia. Previous literature, mainly based on surgical data indicates that up to 90% of cases have a fistula.<sup>6 10 14 17 34–36</sup>

In the present study the knowledge of a trachea-oesophageal fistula is based on the WHO ICD9 and 10 code given by the local registry. All cases with tracheo-oesophageal fistula may not be reported to us using the correct code. However, we used data from all infants and fetuses and not only those that reach the surgeon. In our data we have a slightly lower percentage for tracheo-oesophageal fistula among fetal deaths (68.5%) compared with 71.5% of live births. Our data suggest that the percentage of oesophageal atresia cases with tracheo-oesophageal fistula in the total population of cases with oesophageal atresia is lower than among those surviving until surgery.

During the 20 year study period the prenatal detection rate increased significantly. There was no difference in mortality in the group of cases diagnosed with isolated oesophageal atresia pre or postnatally over time as mortality was low in both groups. In 2004 one or more ultrasound investigations

were offered to all pregnant women in all registries included in this study except for Malta and The Netherlands. All countries offering ultrasound screening had a scan performed in the second trimester of pregnancy.<sup>37</sup>

We found that one third of live born infants with isolated oesophageal atresia were born preterm (gestational age <37 weeks) and if associated anomalies were present, the proportion was even higher. The reported rate of preterm births in the European population ranged from 5.5% to 7.2%.<sup>38 39</sup> The finding of such a high proportion of premature births is probably related to the hydramnion associated with oesophageal atresia.

In 7.8% of all cases termination of pregnancy was performed with the majority of terminations performed for cases with associated anomalies. The terminations may have been due to the severity of the associated anomalies. Some of these associated anomalies such as Edward's syndrome, CHARGE syndrome have a high mortality in the neonatal period. Therefore, comparison of mortality for oesophageal atresia by region may be problematic as the number of termination of pregnancies and the number of live births with associated anomalies may differ between regions and countries depending on laws and policies and prenatal screening programmes.<sup>37</sup>

More than 90% of live births with isolated oesophageal atresia were alive at 1 week of age. The survival rate for live births with associated anomalies was lower. Long-term mortality is reported to be low,<sup>40</sup> but morbidity in childhood is high due to poor growth early in life, recurrent airway infections, chronic lung disease, as well as oesophageal strictures, gastro-oesophageal reflux, swallowing difficulties, and musculoskeletal problems due to either associated anomalies or as a complication to thoracotomy.<sup>6 41–45</sup>

Primary prevention of oesophageal atresia is currently not possible as the aetiology is still unknown. A better understanding of the epidemiology and genetics and a higher prenatal detection rate might contribute to better outcomes as parents and care providers would be better prepared to manage a child with this anomaly.

## CONCLUSIONS

In this study the overall European prevalence of oesophageal atresia was 2.43 per 10 000 births and did not change over time. Large regional differences in the prevalence of oesophageal atresia and in the prenatal detection rate of oesophageal atresia were observed. Prenatal detection rates increased over time. For newborns with isolated oesophageal atresia 1-week survival was excellent although a considerable proportion of these infants were born preterm. Oesophageal atresia is often associated with other major anomalies, congenital heart defects being the most frequent (30% of cases of oesophageal atresia).

The frequency of termination of pregnancy is rather low taking the large number of associated anomalies into consideration. The study enhances the epidemiological information available for oesophageal atresia.

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