



Trisomy 13 and 18: Prevalence and Mortality – a Multi-Registry Population Based Analysis

Journal:	<i>American Journal of Medical Genetics: Part A</i>
Manuscript ID	19-0214.R1
Wiley - Manuscript type:	Original Article
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Keywords:	trisomy 13, trisomy 18, Patau syndrome, Edwards syndrome, trisomies, aneuploidy, congenital anomaly register
Search Terms:	

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3 **Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official*
4 *position of the Centers for Disease Control and Prevention. This analysis has been replicated by Joan K Morris ³. We can*
5 *declare that Dr Saeed Dastgiri ²⁸ is the Programme Director of this hospital-based register (a member of ICBDSR and*
6 *EUROCAT), sole purpose of which is medical research and to collect data on birth defects. Dr Dastgiri is not acting as an*
7 *official representative or on behalf of the Government.*
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For Peer Review

ABSTRACT –

The aim of the study is to determine the prevalence, outcomes and survival [among live births], in pregnancies diagnosed with trisomy 13 (T13) and 18 (T18), by congenital anomaly register and region. Twenty-four population- and hospital-based birth defects surveillance registers from 18 countries, contributed data on T13 and T18 between 1974 and 2014 using a common data-reporting protocol. The mean total birth prevalence [i.e., live births, stillbirths and elective terminations of pregnancies (ETOPFA)] in the registers with ETOPFA (n=15) for T13 was 1.68 (95% CI 1.3-2.06), and for T18 was 4.08 (95% CI 3.01-5.15), per 10,000 births. The prevalence varied among the various registers. The mean prevalence among live births in all registers for T13 was 0.55 (95%CI 0.38-0.72), and for T18 was 1.07 (95% CI 0.77-1.38), per 10,000 births. The median mortality in the first week of life was 48% for T13 and 42% for T18, across all registers, half of which occurred on the first day of life. Across 16 registers with complete one-year follow-up, mortality in first year of life was 87% for T13 and 88% for T18. This study provides an international perspective on prevalence and mortality of T13 and T18. Overall outcomes and survival among live births were poor with about half of live born infants not surviving first week of life; nevertheless about 10% survived the first year of life. Prevalence and outcomes varied by country and termination policies. The study highlights the variation in screening, data collection, and reporting practices for these conditions.

Key words: trisomy 13, trisomy 18, Patau syndrome, Edwards syndrome, aneuploidy, congenital anomaly register, trisomies

Word Count: 250

INTRODUCTION

Trisomy 18 (T18) and trisomy 13 (T13) are the second and third most common autosomal trisomies in live births (LB) after trisomy 21. Previous population prevalence (i.e., total of LB, stillbirths and termination of pregnancies) estimates for T13 range from 1.9 to 2.8 and for T18 from 4.8 to 7 per 10,000 births, from studies in UK and Europe in the last two decades (Loane et al., 2013; Springett et al., 2015; Springett & Morris, 2014; Tonks, Gornall, Larkins, & Gardosi, 2013). The reported live birth prevalence for T13 is 0.43 to 0.54 and for T18 is 0.96 to 1.12 per 10,000 births (Loane et al., 2013). The prevalence is increasing, partly due to increasing maternal age (Loane et al., 2013; Nair, Tucker, Hughes, Greenacre, & Morgan, 2015; Savva, Walker, & Morris, 2010).

Both T13 and T18, also known as Patau and Edwards syndrome, respectively, are associated with a wide range of congenital anomalies, such as cardiac anomalies, orofacial clefts, abdominal wall anomalies, tracheo-esophageal anomalies, genitourinary anomalies, limb and nervous system anomalies (Pont et al., 2006; Springett et al., 2015). This enables many cases to be detected by antenatal ultrasound. A diagnosis can be confirmed with cytogenetic analysis. Many cases are detected during antenatal screening for Down syndrome and through free fetal DNA tests.

T13 and T18 are associated with a poor pregnancy outcome and most live born infants die within the first few days or weeks of life (Loane et al., 2013; Meyer et al., 2016; Springett et al., 2015; Springett & Morris, 2014; Tonks et al., 2013; Wu, Springett, & Morris, 2013). The median survival of live born cases of T13/T18 is reported as 10-14 days with one-year survival around 8-10% (Rasmussen, Wong, Yang, May, & Friedman, 2003; Wu et al., 2013)

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3 There is limited comparative population prevalence and survival data for T13/T18 on an
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5 international basis.
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8 9 **AIM**

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11 The aim of this study was to evaluate the prevalence, natural course, and mortality among
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13 cases with a diagnosis of T13 or T18, across time-periods and different countries. This study
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15 compares infant mortality by congenital anomaly register, region, elective termination of
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17 pregnancy for fetal anomalies (ETOPFA) policy and trends in prevalence over time.
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22 23 **METHODS**

24 25 *Study design and setting*

26
27 This study was undertaken as a part of an International Clearinghouse for Birth Defects
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29 Surveillance and Research (ICBDSR) project to evaluate mortality of significant congenital
30
31 anomalies. The ICBDSR was established in 1974 and is a voluntary non-profit organization
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33 affiliated to the World Health Organization (<http://www.icbdsr.org/>). As a consortium of
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35 birth defects surveillance programs (hereafter referred to as “registers”) from around the
36
37 world, ICBDSR aims to investigate and collaborate in the prevention of birth defects. As of
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39 2019, there are 42 member registers that conduct birth defects surveillance, either
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41 population-based or hospital-based. Of these, 27 contribute, on an annual basis, aggregated
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43 data to ICBDSR for surveillance purposes on children and fetuses affected with one of 39
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45 different birth defects (ICBDSR, 2014). Each register collects, along with selected birth
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47 defects, data on the total annual number of LB and stillbirths (SB) for each of the surveillance
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49 years to aid in estimation of their prevalence.
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3 For the current analysis, the study period included the time between the year a surveillance
4 program was initiated until 2014. Data were requested from the ICBDSR member registries
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6 on the total births per year and the number of T13 and T18 cases per birth year according to:
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- 11 • Pregnancy outcome: LB, SB and ETOPFA
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- 13 • Mortality in LB: Survival at age of 1 day, 1 week, 1 month, 1 year, and more than 1 year
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- 15 • Clinical presentation: isolated or multiple (two or more) major congenital anomalies
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19 *Data quality of registers and statistical methods*

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23 Questionnaires were sent to individual registers to ascertain the type of register (hospital or
24 population-based), ascertainment period, extent of prenatal screening, duration of
25 monitoring, areas covered, ETOPFA policies and follow-up methods for children with birth
26 defects.
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33 The prevalence of T13 and T18 were not calculated for registers that did not report SB
34 (Leoncini et al., 2010), as these estimates were likely to be under-estimates of the true
35 prevalence. Total prevalence estimates were calculated separately for registers with
36 information on LB, SB and ETOPFA and for registers with information on LB and SB only. The
37 reason for exclusion of ETOPFA will influence the accuracy of the total prevalence, as some
38 registers do not include ETOPFA, because terminations are not legally allowed in their
39 regions, whereas others just do not record terminations.
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51 Both total prevalence (i.e., including LB, SB, and ETOPFA) rates per 10,000 total births and
52 live birth prevalence rates per 10,000 total births were calculated for T13 and T18, with
53 corresponding 95% confidence intervals (95% CI). In registers with information on LB, SB and
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3 ETOPFA, three-year rolling averages were calculated for prevalence of T13 and T18,
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5 respectively.
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9 Details about how the registries obtained follow-up information on the survival of live births
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11 with trisomy 13 and trisomy 18, was used to determine if the registry had complete follow-
12
13 up. Registries with incomplete follow-up of LB were excluded from the survival analysis.
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15 Among LB, age-specific mortality was calculated as the number of deaths among live born
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17 cases divided by the total number of infants with T13 and T18, known to be alive at different
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19 time-periods (day of birth, day 2-6, day 7-27, day 28-1 year and 1-4 years) after birth.
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21 Survival probability was calculated using the Kaplan Meier method.
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26 27 **RESULTS**

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30 ICBDSR member registries representing 18 countries in Europe, North America, South
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32 America, and Asia contributed data on cases with T13 (n=23 registers) and T18 (n=24
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34 registers), born between 1974 and 2014 (varying per register). Most registers included all or
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36 part of surveillance years 2001-2014 in their data; 80% of the registers reported data for
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38 2001, 87% for 2009, and 96% included data from 2011 to 2013.
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43 Table 1 A provides details of the 24 individual registers. Eight registers were hospital-based
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45 whereas 16 were population-based (regional or national). All the registers had a method to
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47 screen and follow-up children with birth defects, whether by clinicians or registry staff, at
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49 discharge from hospital or by linkage to administrative databases such as death records or
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51 other health care databases. Some registers had a combination of these methods. Of the 24
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53 registers, 15 registers had information on LB, SB and ETOPFA and nine had information on LB
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55 and SB but not on ETOPFA. Three registers (Iran, Israel and Nuevo Leon) provided no
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57 information on either SB or ETOPFA, thus were excluded from the calculation of total
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3 prevalence rates. Data on mosaicism were not available in individual cases for this study.
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5 Table 1B provides details on the type and duration of follow-up of the surviving live births in
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7 the individual registers.
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10 **Trisomy 13**

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14 Among the 20 registers with information on T13 cases and LB and SB, there were 27,128,565
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16 births and 3128 T13 cases, resulting in a total prevalence of 1.15 per 10,000 total births.
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18 After limiting analysis to the 15 registers with information on LB, SB and ETOPFA (16,793,914
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20 births and 2537 cases of T13), the mean total prevalence was 1.68 per 10,000 births (95% CI
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22 1.3-2.06). This ranged from the highest reported prevalence of 3.0 from the Swedish register
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24 (1999-2014) to the lowest prevalence of 0.7 and 0.8 per 10,000 total births, from Czech and
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26 German registers respectively (Figure 1A). Figure 1B shows the prevalence rates of less than
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28 1/10,000 with a mean of 0.56 (95%CI±0.17) per 10,000 births, from the seven registers
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30 where only LB and SB were reported.
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37 Figure 2A shows T13 pregnancies outcomes (LB, SB or ETOPFA), across all registers. The
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39 proportion of ETOPFA performed was observed to be highest in the European registries. In
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41 countries where ETOPFA is not allowed, the proportion of LB was high, as would be
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43 expected. Data were most complete from 2001-2012, so this period was used to calculate
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45 prevalence rates. Three-year rolling averages in registers where complete information on LB,
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47 SB and ETOPFA was available from 2001-2012 are shown in Figure 2B.
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52 Figure 3 shows the countries and registers arranged in order of decreasing LB prevalence per
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54 10,000 total births (range 0.1 to 2.3). The mean LB prevalence was 0.55 per 10,000 total
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56 births (95% CI 0.38-0.72), with a range from 0.1 (from Italy Lombardy) to 2.3 (from Slovakia).
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3 Figure 4A shows the spectrum of first year mortality among LB for the entire surveillance
4 period for all registers. The median first week mortality was 48% across all registers; first
5 week mortality was highest in Israel (71%), Germany (70%) and USA-Utah (67%). Overall,
6 nearly half of the first week mortality occurred on the first day. The median first year
7 mortality in LB was 87% across 16 registers where complete one-year follow-up data were
8 available – it was highest (94-100%) in Israel, Sweden, Malta, USA-Arkansas and USA-Utah.
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10 Eleven registers had 5-year follow-up data, as shown in Figure 4B and 4C. The cumulative
11 five-year survival for these registers was about 7% (95% CI 0.02-10.02%).
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23 Available data from 15 registers (data not shown) reported that cases associated with major
24 birth defects in addition to T13 resulted in a higher proportion of SB than those without any
25 major birth defects (6.7% vs. 4.2%, p 0.03). Ten registers reported ETOPFA and data on
26 associated major birth defects. Of these, 48.9% T13 cases with birth defects underwent
27 terminations; in comparison, 79.9% T13 cases without any major birth defects were
28 terminated.
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39 **Trisomy 18**

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42 Among the 21 registers with information on T18 cases and LB and SB, there were 27,344,386
43 births and 7184 T18 cases, resulting in a total prevalence of 2.63 per 10,000 total births.
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45 After limiting analysis to the 15 registers with information on LB, SB and ETOPFA (16,982,171
46 births and 6122 cases of T18), the mean total prevalence was 4.08 per 10,000 births (95% CI
47 3.01-5.15). This ranged from the highest reported prevalence of 8.4 from the Paris register
48 and to the lowest prevalence of 0.7 per 10,000 total births from Ukraine register (Figure 5A).
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50 Figure 5B shows the prevalence rates of mean of 1.31 (95%CI±0.94) per 10,000 births, from
51 the eight registers where ETOPFA were not reported.
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3 Figure 6A shows T18 pregnancies outcomes (LB, SB or ETOPFA), across all registers. The
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5 proportion of ETOPFA performed was observed to be highest in the European registries. In
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7 countries where ETOPFA is not allowed, the proportion of LB was understandably high. Data
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9 were the most complete from 2002-2013, so this time-period was used to calculate
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11 prevalence rates. Three-year rolling averages in registers where complete information on LB,
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13 SB and ETOPFA was available from 2002-2013 are shown in figure 6B.
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19 Figure 7 shows the countries and registers arranged in order of decreasing LB prevalence per
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21 10,000 total births (range 0.4 to 3.8). The mean LB prevalence was 1.07 per 10,000 total
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23 births (95% CI 0.77-1.38), with a range from 0.4 (from Mexico RYVEMCE) to 3.8 (from
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25 Slovakia).
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29 Figure 8A shows the spectrum of first year mortality among LB for the entire surveillance
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31 period for all registers. The median first week mortality was 42% across all registers – it was
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33 highest in Sweden (73%), Israel (73%) and Argentina (63%). Nearly half of the first week
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35 mortality occurred on the first day. The median first year mortality in LB was 88% across 16
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37 registers where complete one-year follow-up data were available – it was 100% in Israel,
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39 Sweden, Colombia Cali and Ukraine. Eleven registers had 5-year follow-up data, as shown in
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41 figure 8B and 8C. The cumulative five-year survival for these registers was 7.7% (95% CI 3.97-
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43 14.21%).
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49 Available data from 15 registers (data not shown) reported that cases associated with major
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51 birth defects in addition to T18 resulted in a higher proportion of stillbirths than those
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53 without any major birth defects (12.6% vs. 6.5%, $p < 0.0001$). Ten registers reported ETOPFA
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55 and data on associated major birth defects. Of these, 56.3% T18 cases with birth defects
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3 underwent terminations; in comparison, 84% T18 cases without any major birth defects
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5 were terminated.
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8 9 **DISCUSSION**

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12 This study assessed prevalence in total births, pregnancy outcomes, and mortality among LB,
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14 in T13 and T18 cases, across 24 registers and 18 countries using a standardized protocol. The
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16 quality of data reported varied as three registers only reported LB, while nine did not have
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18 information on ETOPFA. Although the data from some registers goes back as far as 1974,
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20 most of the data were consistently provided between years 2001-2014.
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25 The total prevalence of T13 was 1.15 in the 20 registers and T18 was 2.63 in the 21 registers,
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27 per 10,000 total births that included LB and SB (with or without ETOPFA). Total prevalence
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29 was 1.68 and 4.08 per 10,000 total births, respectively, in the 15 registers that also report
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31 ETOPFA. This is slightly less than the previously reported prevalence estimates of 1.9 - 2.8
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33 and 4.8 - 7 per 10,000 births, respectively, from UK and Europe (Loane et al., 2013; Springett
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35 et al., 2015; Springett & Morris, 2014; Tonks et al., 2013). Our estimates may reflect the
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37 regional variation due to the differences in maternal age, but is more likely to reflect
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39 differences in reporting. Registers that did not report SB and / or ETOPFA had the lowest
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41 prevalence, which is expected as the cases ending in a SB or ETOPFA were excluded. This
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43 may also reflect the overall quality of reporting, as including spontaneous fetal losses
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45 improves the quality of data in congenital anomaly reporting (Leoncini et al., 2010).
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53 In this study, the live birth prevalence of T13 was 0.55 and of T18 was 1.07 per 10,000 births
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55 including data from all registers. This is similar to that reported in other studies (Loane et al.,
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57 2013). As expected, in the countries/regions where ETOPFA is not allowed, the LB
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59 prevalence was higher.
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3 Three-year rolling averages, obtained from the registers reporting all pregnancy outcomes,
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5 showed a gradual rise in total prevalence of cases along with a corresponding rise in ETOPFA,
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7 a decrease in LB and a similar number of SB. These findings may be attributed to increasing
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9 maternal age (Loane et al., 2013; Nair et al., 2015), improved reporting, earlier detection
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11 with prenatal screening programs and parents opting for elective termination of pregnancy.
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16 Almost half of the mortality in LB occurred within the first week and 87-88% by the first year
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18 in both T13 and T18. However, one out of ten cases of T13 and T18 did survive the first year.
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20 This is in agreement with the survival rates reported in other studies (Meyer et al., 2016; Wu
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22 et al., 2013). Earlier studies reported lower one year survival rates of under 10% (Brewer et
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24 al., 2002; Rasmussen et al., 2003; Irving et al., 2011). Data on mosaicism in individual cases
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26 was not available, which may have accounted for some of the survivors. The cumulative five-
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28 year survival rate of around 7% for T13 and 7.7% for T18 was slightly lower than that
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30 recently reported (Meyer et al., 2016 and Nelson et al., 2016), however the confidence
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32 intervals were very wide.
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39 The registers provided data on the presence of major birth defects associated with the
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41 prenatal diagnosis of T13 and T18. As expected, pregnancies with major birth defects in
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43 addition to T13 or T18 resulted in more SB. Interestingly, in cases with isolated diagnosis of
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45 T13 or T18; more terminations were reported than in those with associated birth defects.
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47 This has been reported previously (Springett et al., 2015) and it may be a result of under-
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49 reporting of anomalies in cases where terminations were performed before diagnoses of
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51 major anomalies were made and no pathology was undertaken.
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57 Despite the poor prognosis for T13 and T18, there have been recent reports of long-term
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59 survival of more than five years age (Janvier, Farlow, & Barrington, 2016; Janvier, Farlow, &
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3 Wilfond, 2012; Meyer et al., 2016; Wu et al., 2013). Growing evidence has shown that
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5 medical and surgical interventions can prolong survival (Domingo, Carey, Eckhauser, Wilkes,
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7 & Menon, 2018; Josephsen, Armbrecht, Braddock, & Cibulskis, 2016; Kaneko et al., 2008;
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9 Koshi, Kuniba, Tanikawa, Hashimoto, & Sakurai, 2013; Nelson, Hexem, & Feudtner, 2012;
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11 Nelson, Rosella, Mahant, & Guttman, 2016; Tsukada, Imataka, Suzumura, & Arisaka, 2012).
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13 Regional variations in screening and care for infants with T13 or T18 and differences in
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15 public, parental, or professional perceptions pose ethical challenges for parents and
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17 professionals when encountering a prenatal diagnosis. Cases of longer-term survival, reports
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19 of increased median survival times associated with more interventions, and readily
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21 accessible online patient support groups have influenced attitudes (Janvier et al., 2016;
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23 Janvier et al., 2012; Koshi et al., 2013).
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31 This study has limitations concerning heterogeneity and completeness of the data received
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33 from various registers. The data received included both hospital and population-based
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35 registers, the former representing a selected population whereas the latter representing the
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37 whole region. There was no information on mosaicism, which could have effect on survival
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39 figures, as individuals with mosaicism of T13 and T18 have better survival chances (Wu et al.,
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41 2013). However, this study provides an invaluable global perspective over the years on the
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43 prevalence, pregnancy outcomes and survival of live born infants with T13 and T18. The
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45 prevalence and outcome results highlight the variation in data collection and management
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47 practices in this condition across different regions.
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52 53 **Acknowledgement:**

54
55 Results from Slovakia originated in cooperation with National Health Information Center in
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57 Bratislava.

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59 The work conducted at the ECEMC group was supported by the Instituto de Salud Carlos III
60
(ISCIII, Ministry of Science, Innovation and Universities) of Spain, and the Fundación 1000

sobre Defectos Congénitos of Spain. Components of ECEMC's Peripheral Group are gratefully acknowledged.

Conflict of interest: None to declare

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Figure legends:

Figure 1. Total prevalence data for Trisomy 13 (1974-2015) from all registers A) with complete data on LB, SB and ETOPFA; B) with data only on LB and SB

Figure 2. A) Pregnancy outcomes in all registers in Trisomy 13 between 1974-2015; B) Three-year rolling averages for prevalence of Trisomy 13 in registers where ETOPFA is reported (2001-2012)

Figure 3. Live birth prevalence in all registers in Trisomy 13 (1974-2015)

Figure 4. Mortality in live births (Trisomy 13) A) One year follow-up data in all registers*; B) Five year follow-up in registers where outcomes were known; C) First year mortality from figure 4B shown in further detail (dotted line represent 95% CI)

Figure 5. Total prevalence data for Trisomy 18 (1974-2015) from all registers A) with complete data on LB, SB and ETOPFA; B) with data only on LB and SB

Figure 6. A) Pregnancy outcomes in all registers in Trisomy 18 between 1974-2015; B) Three-year rolling averages for prevalence of Trisomy 18 in registers where ETOPFA is reported (2002-2013)

Figure 7. Live birth prevalence in all registers in Trisomy 18 (1974-2015)

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2
3 Figure 8. Mortality in live births (Trisomy 18) A) One year follow-up data in all registers*; B) Five year
4 follow-up in registers where outcomes were known; C) First year mortality from figure 8B shown in
5 further detail (dotted line represent 95% CI)
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Table 1A. Trisomy 13 and 18 mortality surveillance period by continent, country, and register (ICBDSR 1974-2015)

Continent	Country	Register	Type of Program	Maximum age at diagnosis	ETOPFA Reported/Allowed	Period of study	Total Years	Trisomy 13 n	Trisomy 18 n
S. America	Argentina	RENAC	Hospital-based	Hospital discharge	Not allowed	2009-2014	6	42	119
	Colombia	Bogota	Hospital-based	Hospital discharge	Not reported~	2001-2014	14	24	28
		Cali	Hospital-based	Hospital discharge	Not reported~	2011-2014	4	-	7
	S. America	ECLAMC	Hospital-based	Hospital discharge	Not allowed	1995-2014	20	237	538
Europe	Czech Rep	NR	Population-based	Upto 15 years	Yes	1994-2014	21	150	469
	France	Paris	Population-based	28 days	Yes	1981-2014	34	251	736
	Germany	Saxony-Anhalt	Population-based	1 year	Yes	1980-2014	35	43	125
	Italy	Lombardy	Population-based	6 years	Yes	2003-2012	10	17	58
		Tuscany	Population-based	1 year	Yes	1992-2014	23	88	252
	Malta	MCAR	Population-based	1 year	Not allowed	1995-2013	19	6	29
	Netherlands	North	Population-based	10 years	Yes	1991-2014	34	78	239
	Slovakia	STIC	Population-based	1 year	Yes	2001-2013	13	30	51
		Spain ECEMC	with TOPFA	Hospital-based	3 days	Since 1985 & reported**	1995-2013	19	93
	no TOPFA		Hospital-based	3 days	Since 1985 & not reported	1986-2013	28	91	150
	Sweden	No TOPFA	Population-based	28 days***	Not allowed	1974-1998	25	154	133
		with TOPFA	Population-based	1 year	Since 1999	1999-2014	16	485	1202
	Ukraine*	OMNI-Net	Population-based	1 year	Yes	2000-2013	14	25	27
UK	Wales CARIS	Population-based	Upto 18 years	Yes	1998-2014	17	117	310	
N America	Mexico	Nuevo Leon	Population-based	6 days	Not allowed	2011-2015	5	22	61
		RYVEMCE	Hospital-based	3 days	Not allowed	1979-2013	36	37	58
	USA	Arkansas	Population-based	2 years	Yes	1993-2012	20	81	167
		Atlanta	Population-based	6 years	Yes	1974-2008	35	213	415
		Texas	Population-based	1 year	Yes	1996-2012	17	716	1517
Utah	Population-based	2 years	Yes	1994-2012	19	150	316		
Asia	Iran	TROCA	Hospital-based	1 year	Not reported	2008-2012	5	6	7
	Israel	IBDSP	Hospital-based	Hospital discharge	Not reported	2000-2014	15	14	11

ETOPFA = Elective termination of pregnancies for fetal anomalies; **n** = number of cases reported; **Data only available from 1995 onwards;***After 1987 till 1 year; ~ETOPFA legal since 2006; **Name of Register:** RENAC= National Network of Congenital Anomalies of Argentina; ECLAMC= Latin American Collaborative Study of Congenital Malformations; NR= National Register; MCAR= Malta Congenital Anomalies Registry; STIC= Slovak Teratology Information Center; ECEMC= Spanish Collaborative Study of Congenital Malformations; *OMNI-Net= Ukraine Birth Defects Prevention Program [Rivne (for T13 and T18) and Volyn (for T18 only) Provinces]; CARIS= Congenital Anomaly Register & Information Systems for Wales, UK; RYVEMCE= Mexican Registry and Epidemiological Surveillance of External Congenital Malformations; TROCA= Tabriz Registry of Congenital Anomalies; IBDSP= Israel birth defect surveillance and research program; UK= United Kingdom; USA= United States of America.

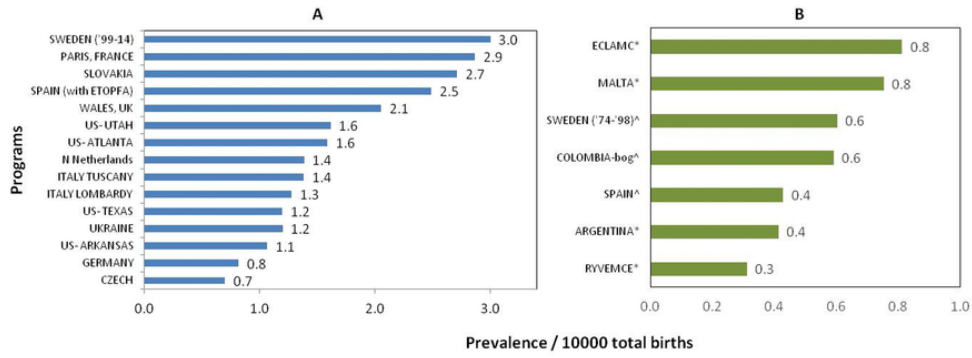
Table 1B. Description of follow-up methods for live births from registers contributing to the ICBDSR

Country-Register	Follow-up until discharge from the maternity hospital	Follow-up by a clinician or registry staff	Linkage with death certificates	Maximum follow-up period reported in study
Argentina-RENAC	Yes	Yes	No	1-6 days
Colombia-Bogotá	Yes	Yes	No	1 day
Colombia-Cali	Yes	Yes	No	No mortality reported for live births
South America-ECLAMC	Yes	Yes	No	28 days-11 months
Czech Republic - NR	No	No	Yes	≥5 years
France-Paris	Yes	Yes	No	7-27 days
Germany-Saxony Anhalt	Yes	Yes ²	No	1-5 years
Italy-Lombardy	No	No	Yes, 2003 up to 2015	1-4 years
Italy-Tuscany	No	No	Yes, 1992 up to 2015	28 days-11 months
Malta-MCAR	Yes ¹	Yes	Yes ⁴	1-4 years
Netherlands-Northern	Yes	Yes	No	≥5 years
Slovak Republic - STIC	Yes	No	No	1-6 days
Spain-ECEMC	Yes	No	No	1-6 days
Sweden	No	No	Yes, 1974 up to April 2016	≥5 years
UK-Wales - CARIS	Yes	No	Yes, to GP system, till 18 years	≥ 5 years
Ukraine-OMNI-Net*	Yes	Yes	No	1-5 years
Mexico-Nuevo León	Yes	No	No	1 year
Mexico-RYVEMCE	Yes	No	No	1-6 days
USA-Arkansas	Yes	No	Yes, 1993 up to 2015	≥5 years
USA-Atlanta	Yes	No	Yes, 1979 up to 2008	≥5 years
USA-Texas	Yes	No	Yes, 1996 up to 2013	≥5 years
USA-Utah	Yes	No	Yes, until age 2	≥5 years
Iran-TROCA	Yes	Yes ³	No	1-6 days
Israel-IBDSP	Yes	No	Yes, 2000 up to 2014	1-4 years

¹babies are followed up until discharge and their hospital files are again seen at 1 year of age, linkage with mortality data continues indefinitely; ²until 18 years; ³children in university hospital(s); ⁴continuous linkage with mortality register

Name of Register: RENAC= National Network of Congenital Anomalies of Argentina; ECLAMC= Latin American Collaborative Study of Congenital Malformations; NR= National Register; MCAR= Malta Congenital Anomalies Registry; STIC= Slovak Teratology Information Center; ECEMC= Spanish Collaborative Study of Congenital Malformations; *OMNI-Net= Ukraine Birth Defects Prevention Program [Rivne (for T13 and T18) and Volyn (for T18 only) Provinces]; CARIS= Congenital Anomaly Register & Information Systems for Wales, UK; RYVEMCE= Mexican Registry and Epidemiological Surveillance of External Congenital Malformations; TROCA= Tabriz Registry of Congenital Anomalies; IBDSP= Israel birth defect surveillance and research program; UK= United Kingdom; USA= United States of America.

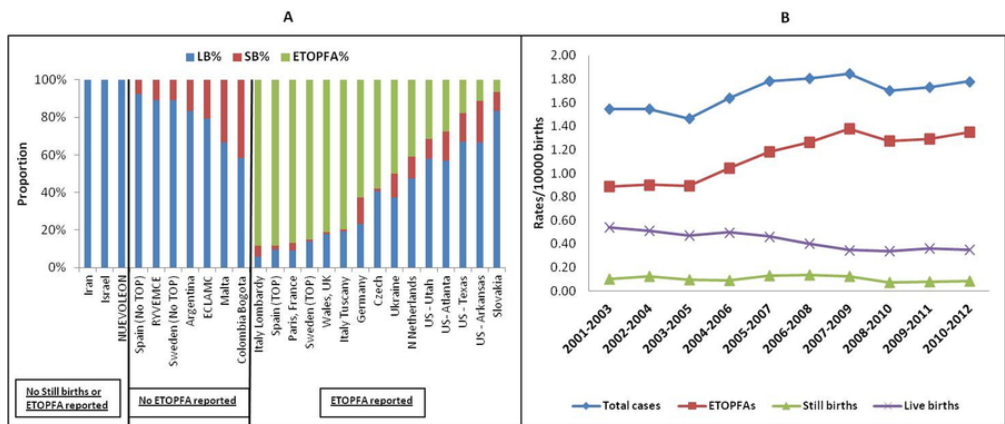
Figure 1. Total prevalence data for Trisomy 13 (1974-2015) from all registers
 A) with complete data on LB, SB and ETOPFA; B) with data only on LB and SB



* ETOPFA is not allowed in these regions; ^ ETOPFA was not reported in these regions; (This graph excludes three registers where no SB were reported)
 LB = live births; SB = still births; ETOPFA = Elective Termination of Pregnancy for Fetal Anomalies

76x35mm (300 x 300 DPI)

Figure 2. A) Pregnancy outcomes in all registers in Trisomy 13 between 1974-2015; B) Three-year rolling averages for prevalence of Trisomy 13 in registers where ETOFPA is reported (2001-2012)

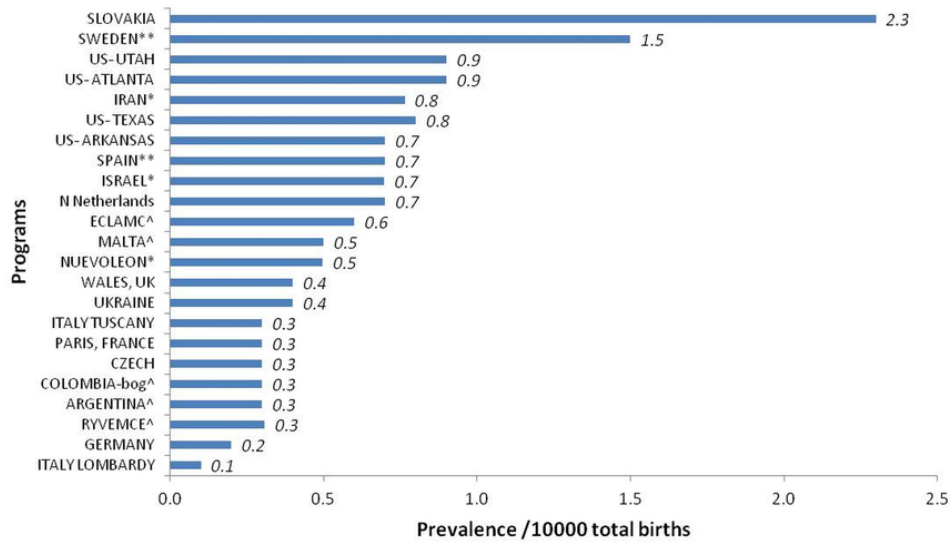


LB = live births; SB = still births; ETOFPA /TOP= Elective Termination of Pregnancy for Fetal Anomalies

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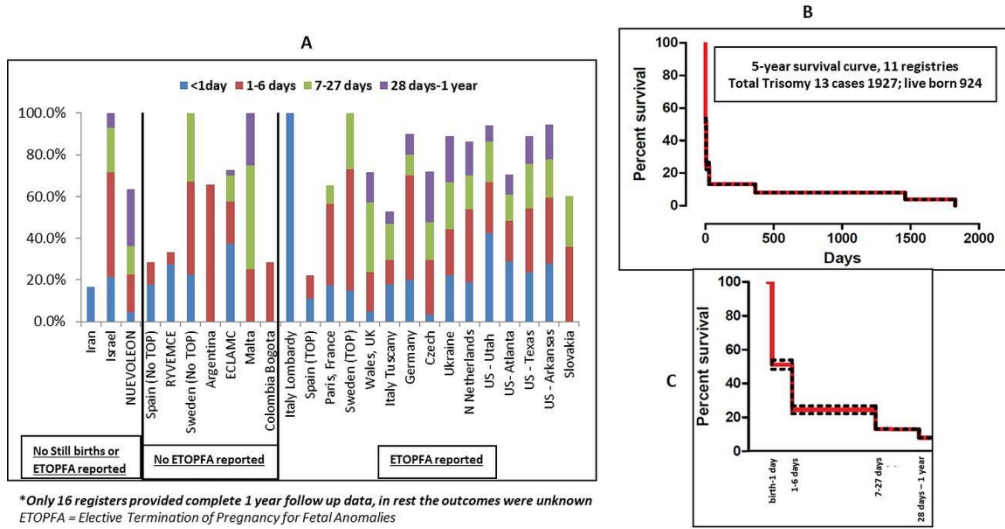
Figure 3. Live birth prevalence in all registers in Trisomy 13 (1974-2015)



[^] ETOPFA is not allowed in these regions; [^] SB and ETOPFA was not reported in these regions
^{**} Combined data of all years of reporting (before and after ETOPFA was reported)

76x49mm (300 x 300 DPI)

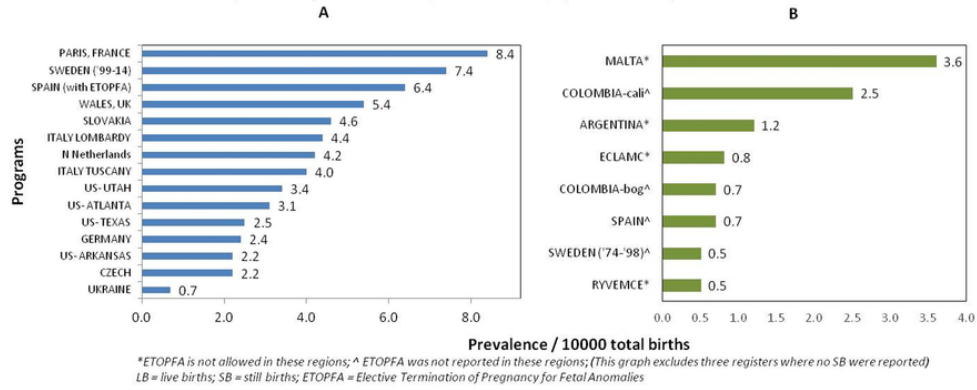
Figure 4. Mortality in live births (Trisomy 13)
 A) One year follow-up data in all registers* B) Five year follow-up in registers where outcomes were known
 C) First year mortality from figure 4B shown in further detail (dotted line represent 95% CI)



*Only 16 registers provided complete 1 year follow up data, in rest the outcomes were unknown
 ETOPFA = Elective Termination of Pregnancy for Fetal Anomalies

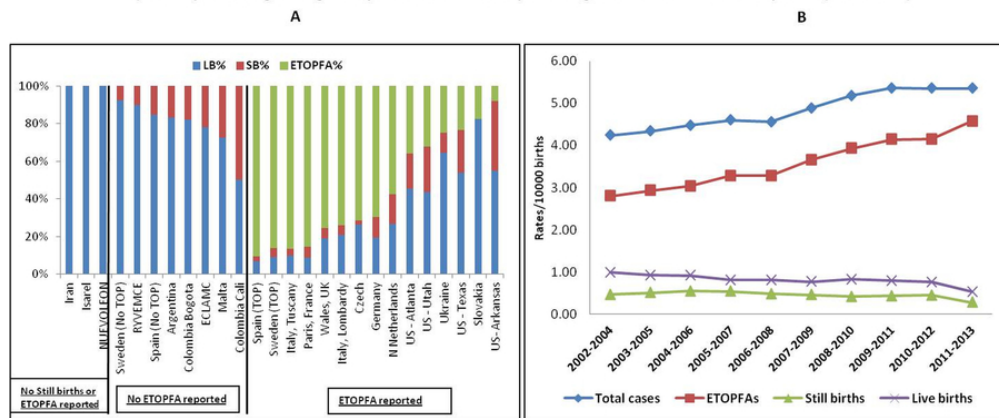
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Figure 5. Total prevalence data for Trisomy 18 (1974-2015) from all registers
 A) with complete data on LB, SB and ETOFPA; B) with data only on LB and SB



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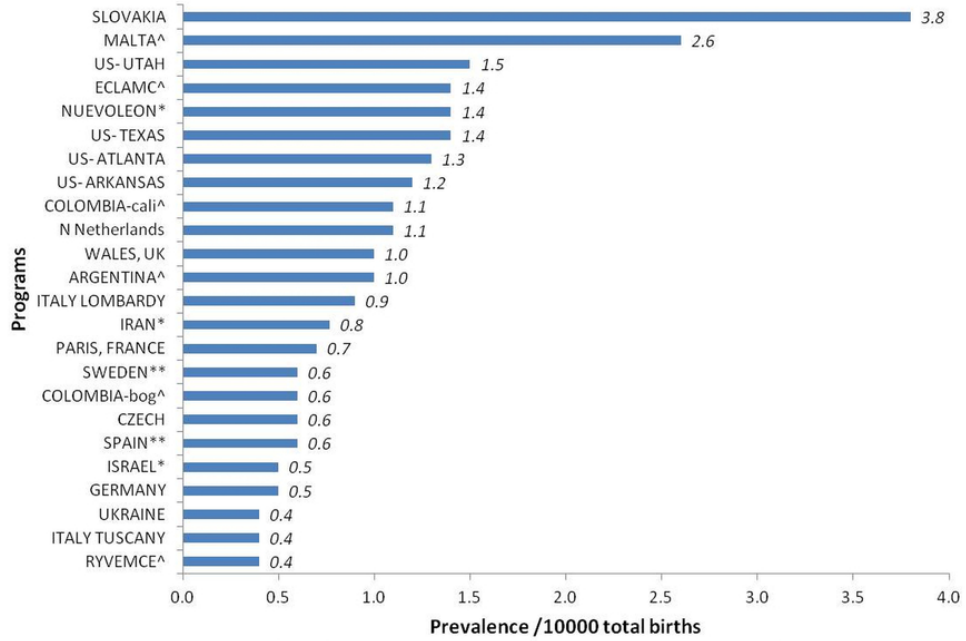
Figure 6. A) Pregnancy outcomes in all registers in Trisomy 18 between 1974-2015;
 B) Three-year rolling averages for prevalence of Trisomy 18 in registers where ETOPFA is reported (2002-2013)



LB = live births; SB = still births; ETOPFA/TOP = Elective Termination of Pregnancy for Fetal Anomalies

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Figure 7. Live birth prevalence in all registers in Trisomy 18 (1974-2015)

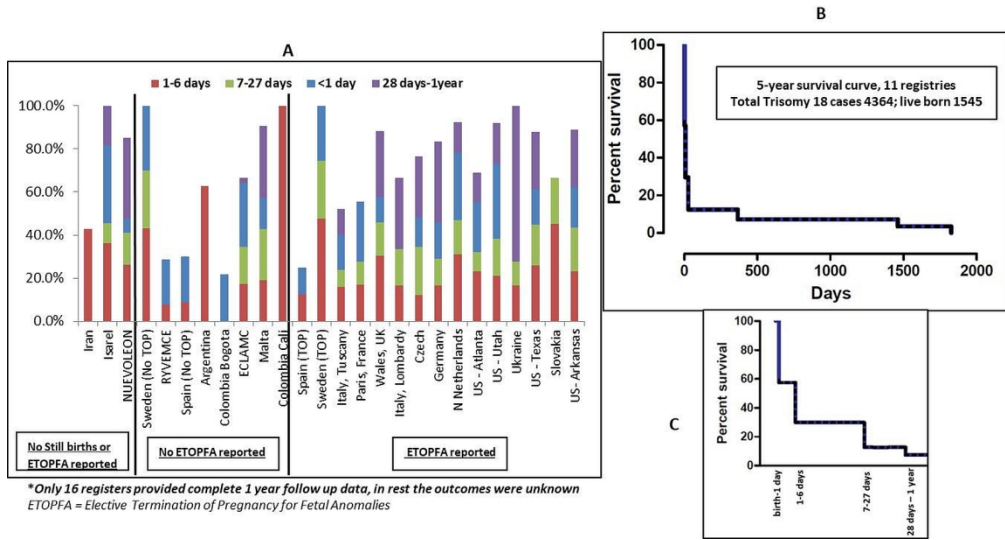


[^] ETOPFA is not allowed in these regions; [^] SB and ETOPFA was not reported in these regions

^{**} Combined data of all years of reporting (before and after ETOPFA was reported)

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Figure 8. Mortality in live births (Trisomy 18)
A) One year follow-up data in all registers* B) Five year follow-up in registers where outcomes were known
C) First year mortality from figure 8B shown in further detail (dotted line represent 95% CI)



152x93mm (300 x 300 DPI)

Trisomy 13 and 18 – Prevalence and Mortality – a Multi-Registry Population Based Analysis

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3 **Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official*
4 *position of the Centers for Disease Control and Prevention. This analysis has been replicated by Joan K Morris ³.We can*
5 *declare that Dr Saeed Dastgiri ²⁸ is the Programme Director of this hospital-based register (a member of ICBDSR and*
6 *EUROCAT), sole purpose of which is medical research and to collect data on birth defects. Dr Dastgiri is not acting as an*
7 *official representative or on behalf of the Government.*
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For Peer Review

ABSTRACT –

Objectives: ~~The aim of the study is~~ ~~To~~ determine the prevalence, outcomes and survival [among live births], in pregnancies diagnosed with ~~t~~Trisomy 13 (T13) and 18 (T18), by congenital anomaly register and region.

Methods: ~~Twenty-four population- and hospital-based birth defects surveillance registers from 18 countries, contributed data on T13 and T18 between 1974 and 2014 using a common data-~~reporting protocol.

Results: The mean total birth prevalence [i.e., live births, stillbirths and elective terminations of pregnancies (ETOPFA)] in the registers with ETOPFA (n=15) for T13 was 1.68 (95% CI 1.3-2.06), and for T18 was 4.08 (95% CI 3.01-5.15), per 10,000 births. The prevalence varied among the various registers. The mean prevalence among live births in all registers for T13 was 0.55 (95%CI 0.38-0.72), and for T18 was 1.07 (95% CI 0.77-1.38), per 10,000 births. The median mortality in the first week of life was 48% for T13 and 42% for T18, across all registers, half of which occurred on the first day of life. Across 16 registers with complete one-year follow-up, mortality in first year of life was 87% for T13 and 88% for T18.

Conclusions: This study provides an international perspective on prevalence and mortality of T13 and T18. Overall outcomes and survival among live births were poor with about half of live born infants not surviving the first week of life; ~~however-~~nevertheless about 10% survived the first year of life. Prevalence and outcomes varied by country and termination policies. The study highlights the variation in screening, data collection, and reporting practices for these conditions.

Key words: trisomy 13, trisomy 18, Patau syndrome, Edwards syndrome, aneuploidy, congenital anomaly register, trisomies

Word Count: 250

~~Introduction~~ INTRODUCTION

Trisomy 18 (T18) and ~~t~~Trisomy 13 (T13) are the second and third most common autosomal trisomies in live births (LB) after trisomy 21. Previous population prevalence (i.e., total of LB, stillbirths and termination of pregnancies) estimates for T13 range from 1.9 to 2.8 and for T18 from 4.8 to 7 per 10,000 births, from studies in UK and Europe in the last two decades (Loane et al., 2013; ~~A.~~Springett et al., 2015; ~~A.L.~~Springett & Morris, 2014; Tonks, Gornall, Larkins, & Gardosi, 2013). The reported live birth prevalence for T13 is 0.43 to 0.54 and for T18 is 0.96 to 1.12 per 10,000 births (Loane et al., 2013). The prevalence is increasing, partly due to increasing maternal age (Loane et al., 2013; Nair, Tucker, Hughes, Greenacre, & Morgan, 2015; Savva, Walker, & Morris, 2010).

Both T13 and T18, also known as Patau's and Edward's syndrome, respectively, are associated with a wide range of congenital anomalies, such as cardiac anomalies, orofacial clefts, abdominal wall anomalies, tracheo-esophageal anomalies, genitourinary anomalies, limb and nervous system anomalies (Pont et al., 2006; ~~A.~~Springett et al., 2015). This enables many cases to be detected by antenatal ultrasound. A diagnosis can be confirmed with cytogenetic analysis. Many cases are detected during antenatal screening for Down syndrome and through free fetal DNA tests.

T13 and T18 are associated with a poor pregnancy outcome and most live born infants die within the first few days or weeks of life (Loane et al., 2013; Meyer et al., 2016; ~~A.~~Springett et al., 2015; ~~A.L.~~Springett & Morris, 2014; Tonks et al., 2013; Wu, Springett, & Morris, 2013). The median survival of live born cases of T13/T18 is reported as 10-14 days with one-year survival around 8-10% (Rasmussen, Wong, Yang, May, & Friedman, 2003; Wu et al.,

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3 2013) There is limited comparative population prevalence and survival data for T13/T18 on
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5 an international basis.
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8 **AimAIM**

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12 The aim of this study was to evaluate the prevalence, natural course, and mortality among
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14 cases with a diagnosis of T13 or T18, across time-periods and different countries. This study
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16 compares infant mortality by congenital anomaly register, region, elective termination of
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18 pregnancy for fetal anomalies (ETOPFA) policy and trends in prevalence over time.
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22 **MethodsMETHODS**

23 *Study design and setting*

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29 This study was undertaken as a part of an International Clearinghouse for Birth Defects
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31 Surveillance and Research (ICBDSR) project to evaluate mortality of significant congenital
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33 anomalies. The ICBDSR was established in 1974 and is a voluntary non-profit organization
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35 affiliated to the World Health Organization (<http://www.icbdsr.org/>). As a consortium of
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37 birth defects surveillance programs (hereafter referred to as “registers”) from around the
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39 world, ICBDSR aims to investigate and collaborate in the prevention of birth defects. As of
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41 2019, there are 42 member registers that conduct birth defects surveillance, either
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43 population-based or hospital-based, ~~of which~~ Of these 27 contribute, on an annual basis,
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45 aggregated data to ICBDSR for surveillance purposes on children and fetuses affected with
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47 one of 39 different birth defects (ICBDSR, 2014). Each register collects, along with selected
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49 birth defects, data on the total annual number of LB and stillbirths (SB) for each of the
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51 surveillance years to aid in estimation of their prevalence.
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3 For the current analysis, the study period included the time between the year a surveillance
4 program was initiated until 2014. Data were requested from the ICBDSR member registries
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6 on the total births per year and the number of T13 and T18 cases per birth year according to:
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11 • Pregnancy outcome: LB, SB and ETOFPA
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13 • Mortality in LB: Survival at age of 1 day, 1 week, 1 month, 1 year, and more than 1 year
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15 • Clinical presentation: isolated or multiple (two or more) major congenital anomalies
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20 *Data quality of registers and statistical methods*
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23 Questionnaires were sent to individual registers to ascertain the type of register (hospital or
24 population-based), ascertainment period, extent of prenatal screening, ~~details of their~~
25 ~~registries,~~ duration of monitoring, areas covered, ETOFPA policies and follow-up methods for
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27 children with birth defects.
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33 The prevalence of T13 and T18 were not calculated for registers that did not report SB
34 (Leoncini et al., 2010), as these estimates were likely to be under-estimates of the true
35 prevalence. Total prevalence estimates were calculated separately for registers with
36 information on LB, SB and ETOFPA and for registers with information on LB and SB only. The
37 reason for exclusion of ETOFPA will influence the accuracy of the total prevalence, as some
38 registers do not include ETOFPA, because terminations are not legally allowed in their
39 regions, whereas others just do not record terminations.
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51 Both total prevalence (i.e., including LB, SB, and ETOFPA) rates per 10,000 total births and
52 live birth prevalence rates per 10,000 total births were calculated for T13 and T18, with
53 corresponding 95% confidence intervals (95% CI). ~~Total prevalence estimates were also~~
54 ~~calculated separately for registers with information on LB, SB and ETOFPA and for registers~~
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3 ~~with information on LB and SB only. Registers with no information on SB or ETOPFA were~~
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5 ~~excluded from calculations for total prevalence rates.~~ In registers with information on LB, SB
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8 and ETOPFA, three-year rolling averages were calculated for prevalence of T13 and T18,
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10 respectively. ~~The validity of the data were determined by whether or not SB were reported~~
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12 ~~(Leoncini et al., 2010).~~

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16 Details about how the registries obtained follow-up information on the survival of live births
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18 with trisomy 13 and trisomy 18, was used to determine if the registry had complete follow-
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20 up. Registries with incomplete follow-up of LB were excluded from the survival analysis.

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24 Among LB, age-specific mortality was calculated as the number of deaths among live born
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26 cases divided by ~~a the~~ total number of ~~live born~~ infants with T13 and T18, known to be alive
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28 at different time-periods (day of birth, day 2-6, day 7-27, day 28-1 year and 1-4 years) after
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30 birth. Survival probability was calculated using the Kaplan Meier method.~~by comparing the~~
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32 ~~total number of LB with T13 and T18, with the cumulative proportion of cases that died at~~
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34 ~~different ages as mentioned above (set at 100% at birth). Registries with incomplete follow-~~
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36 ~~up of LB were excluded from the survival analysis.~~

41 42 **Results** RESULTS

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45 ICBDSR member registries representing 18 countries in Europe, North America, South
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47 America, and Asia contributed data on cases with T13 (n=23 registers) and T18 (n=24
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49 registers), born between 1974 and 2014 (varying per register). Most registers included all or
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51 part of surveillance years 2001-2014 in their data; 80% of the registers reported data for
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53 2001, 87% for 2009, and 96% included data from 2011 to 2013.
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3 Table 1 A ~~outlines the~~ provides details of the 24 individual registers. Eight registers were
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5 hospital-based whereas 16 were population-based (regional or national). All the registers
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7 had a method to screen and follow-up children with birth defects, whether by clinicians or
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9 registry staff, at discharge from hospital or by linkage to administrative databases such as
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11 death records or other health care databases. Some registers had a combination of these
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13 methods. Of the 24 registers, 15 registers had information on LB, SB and ETOPFA and nine
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15 ~~did not have~~ had information on LB and SB but not on ETOPFA. Three registers (Iran, Israel
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17 and Nuevo Leon) provided no information on either SB or ETOPFA, thus were excluded from
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19 the calculation of total prevalence rates. Data on mosaicism were not available in
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21 individual cases for this study. Table 1B provides details on the type and duration of follow-
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23 up of the surviving live births in the individual registers.
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31 **Trisomy 13**

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34 Among the 20 registers with information on T13 cases and LB and SB, there were 27,128,565
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36 births and 3128 T13 cases, resulting in a total prevalence of 1.15 per 10,000 total births.
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38 After ~~restricting limiting analysis~~ to the 15 registers with information on LB, SB and ETOPFA
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40 (16,793,914 births and 2537 cases of T13), the mean total prevalence was 1.68 per 10,000
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42 births (95% CI 1.3-2.06). This ranged from the highest reported prevalence of 3.0 from the
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44 Swedish register (1999-2014) to the lowest prevalence of 0.7 and 0.8 per 10,000 total births,
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46 from Czech and German registers respectively (Figure 1A). Figure 1B shows the prevalence
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48 rates of less than 1/10,000 with a mean of 0.56 (95%CI±0.17) per 10,000 births, from the
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50 seven registers where only LB and SB were reported.
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57 Figure 2A shows T13 pregnancies outcomes (LB, SB or ETOPFA), across all registers. The
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59 proportion of ETOPFA performed was observed to be ~~the~~ highest in the European registries.
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3 In countries where ETOPFA is not allowed, ~~logically~~ the proportion of LB was high, as would
4 be expected. Data ~~were~~ was most complete from 2001-2012, so this period was used to
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6 calculate prevalence rates. Three-year rolling averages in registers where complete
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8 information on LB, SB and ETOPFA was available from 2001-2012 are shown in Figure 2B.
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13 Figure 3 shows the countries and registers arranged in order of decreasing LB prevalence per
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15 10,000 total births (range 0.1 to 2.3). The mean LB prevalence was 0.55 per 10,000 total
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17 births (95% CI 0.38-0.72), with a range from 0.1 (from Italy Lombardy) to 2.3 (from Slovakia).
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22 Figure 4A shows the spectrum of first year mortality among LB for the entire surveillance
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24 period for all registers. The median first week mortality was 48% across all registers; first
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26 week mortality was highest in Israel (71%), Germany (70%) and USA-Utah (67%). Overall,
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28 nearly half of the first week mortality occurred on the first day. The median first year
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30 mortality in LB was 87% across 16 registers where complete one-year follow-up data ~~were~~ was
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32 available – it was highest (94-100%) in Israel, Sweden, Malta, USA-Arkansas and USA-Utah.
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36 ~~Ten-Eleven~~ registers had 5-year follow-up data, as shown in Figure 4B and 4C. ~~The~~ shows
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38 cumulative five-year survival for these ~~ten registries~~ registers ~~was about 7% (95% CI 0.02-~~
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40 10.02%).
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45 Available data from 15 registers (data not shown) reported that cases associated with major
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47 birth defects in addition to T13 resulted in a higher proportion of SB than those without any
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49 major birth defects (6.7% vs. 4.2%, p 0.03). Ten registers reported ETOPFA and data on
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51 associated major birth defects. Of these, 48.9% T13 cases with birth defects underwent
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53 terminations; in comparison, 79.9% T13 cases without any major birth defects were
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55 terminated.
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60 **Trisomy 18**

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3 Among the 21 registers with information on T18 cases and LB and SB, there were 27,344,386
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5 births and 7184 T18 cases, resulting in a total prevalence of 2.63 per 10,000 total births.
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8 After restricting-limiting analysis to the 15 registers with information on LB, SB and ETOPFA
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10 (16,982,171 births and 6122 cases of T18), the mean total prevalence was 4.08 per 10,000
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12 births (95% CI 3.01-5.15). This ranged from the highest reported prevalence of 8.4 from the
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14 Paris register and to the lowest prevalence of 0.7 per 10,000 total births from Ukraine
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16 register (Figure 5A). Figure 5B shows the prevalence rates of mean of 1.31 (95%CI±0.94) per
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18 10,000 births, from the eight registers where ETOPFA were not reported.
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23 Figure 6A shows T18 pregnancies outcomes (LB, SB or ETOPFA), across all registers. The
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25 proportion of ETOPFA performed was observed to be ~~the~~ highest in the European registries.
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27 In countries where ETOPFA is not allowed, the proportion of LB was logically-understandably
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29 high. Data were the most complete from 2002-2013, so this time-period was used to
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31 calculate prevalence rates. Three-year rolling averages in registers where complete
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33 information on LB, SB and ETOPFA was available from 2002-2013 are shown in figure 6B.
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39 Figure 7 shows the countries and registers arranged in order of decreasing LB prevalence per
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41 10,000 total births (range 0.4 to 3.8). The mean LB prevalence was 1.07 per 10,000 total
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43 births (95% CI 0.77-1.38), with a range from 0.4 (from Mexico RYVEMCE) to 3.8 (from
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45 Slovakia).
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49 Figure 8A shows the spectrum of first year mortality among LB for the entire surveillance
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51 period for all registers. The median first week mortality was 42% across all registers – it was
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53 highest in Sweden (73%), Israel (73%) and Argentina (63%). Nearly half of the first week
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55 mortality occurred on the first day. The median first year mortality in LB was 88% across 16
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57 registers where complete one-year follow-up data were available – it was 100% in Israel,
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3 Sweden, Colombia Cali and Ukraine. ~~Ten~~ Eleven registers had 5-year follow-up data, as
4 shown in figure. ~~Figure~~ 8B and 8C. ~~The show~~ cumulative five-year survival for these ~~ten~~
5 registers was 7.7% (95% CI 3.97-14.21%). -
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11 Available data from 15 registers (data not shown) reported that cases associated with major
12 birth defects in addition to T18 resulted in a higher proportion of stillbirths than those
13 without any major birth defects (12.6% vs. 6.5%, $p < 0.0001$). Ten registers reported ETOPFA
14 and data on associated major birth defects. Of these, 56.3% T18 cases with birth defects
15 underwent terminations; in comparison, 84% T18 cases without any major birth defects
16 were terminated.
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26 ~~Discussion~~ DISCUSSION

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30 This study assessed prevalence in total births, pregnancy outcomes, and mortality among LB,
31 in T13 and T18 cases, across 24 registers and 18 countries using a standardized protocol. The
32 quality of data reported varied as three registers only reported LB, while nine did not have
33 information on ETOPFA. Although the data from some registers goes back as far as 1974,
34 most of the data were consistently provided between years 2001-2014.
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43 The total prevalence of T13 was 1.15 in the 20 registers and T18 was 2.63 in the 21 registers,
44 per 10,000 total births that included LB and SB (with or without ETOPFA). Total prevalence
45 was 1.68 and 4.08 per 10,000 total births, respectively, in the 15 registers that also report
46 ETOPFA. This is slightly less than the previously reported prevalence estimates of 1.9 - 2.8
47 and 4.8 - 7 per 10,000 births, respectively, from UK and Europe (Loane et al., 2013; ~~A.~~
48 Springett et al., 2015; ~~A.L.~~ Springett & Morris, 2014; Tonks et al., 2013). Our estimates may
49 reflect the regional variation due to differences in maternal age, but is more likely to reflect
50 and differences in reporting. Registers that did not report SB and / or ETOPFA had the lowest
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3 ~~prevalence~~prevalence, which is expected as the cases ending in a SB or ETOPFA were
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5 ~~excluded. This, which~~ may also reflect the overall quality of reporting, as ~~has been previously~~
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7 ~~suggested that~~ including spontaneous fetal losses improves the quality of data in congenital
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9 anomaly reporting (Leoncini et al., 2010).
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14 In this study, the live birth prevalence of T13 was 0.55 and of T18 was 1.07 per 10,000 births
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16 including data from all registers. This is similar to that reported in other studies (Loane et al.,
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18 2013). As expected, in the countries/regions where ETOPFA is not allowed, the LB
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20 prevalence was higher.
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24 Three-year rolling averages, obtained from the ~~most complete data from~~ registers reporting
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26 all ~~the~~ pregnancy outcomes, showed a gradual rise in total prevalence of cases along with
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28 ~~the a~~ corresponding rise in ETOPFA, a decrease in LB and a similar number of SB. These
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30 findings may be attributed to increasing maternal age (Loane et al., 2013; Nair et al., 2015),
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32 improved reporting, earlier detection with prenatal screening programs and parents opting
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34 for elective termination of pregnancy.
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40 Almost half of the mortality in LB occurred within the first week and 87-88% by the first year
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42 in both T13 and T18. However, one out of ten cases of T13 and T18 did survive the first year.
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44 This is in agreement with the ~~poor~~ survival rates reported in other studies (Meyer et al.,
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46 2016; ~~Rasmussen et al., 2003;~~ Wu et al., 2013). Earlier studies reported lower one year
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48 survival rates of under 10% (Brewer et al., 2002; Rasmussen et al., 2003; Irving et al., 2011).
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50 ~~However, one out of ten cases of T13 and T18 did survive the first year.~~ Data on mosaicism
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52 in individual cases ~~was were~~ not available, which may have accounted for some of the
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54 survivors. The cumulative five-year survival rate of around 7% for T13 and 7.7% for T18 was
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3 slightly lower than that recently reported (Meyer et al., 2016 and Nelson et al., 2016),
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5 however the confidence intervals were very wide.
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9 The registers provided data on ~~whether there were~~the presence of major birth defects
10 associated with the prenatal diagnosis of T13 and T18. As expected, pregnancies with major
11 birth defects in addition to T13 or T18 resulted in more SB. Interestingly, in cases with
12 isolated diagnosis of T13 or T18; more terminations were reported than in those with
13 associated birth defects. This has been reported previously (Springett et al., 2015) and it may
14 be a result of under-reporting of anomalies in cases where terminations were performed
15 before diagnoses of major anomalies were made and no pathology was undertaken.
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27 Despite the poor prognosis for T13 and T18, there have been recent reports of long-term
28 survival of more than five years age (Janvier, Farlow, & Barrington, 2016; Janvier, Farlow, &
29 Wilfond, 2012; Meyer et al., 2016; Wu et al., 2013). Growing evidence has shown that
30 medical and surgical interventions can prolong survival (Domingo, Carey, Eckhauser, Wilkes,
31 & Menon, 2018; Josephsen, Armbrecht, Braddock, & Cibulskis, 2016; Kaneko et al., 2008;
32 Kosho, Kuniba, Tanikawa, Hashimoto, & Sakurai, 2013; Nelson, Hexem, & Feudtner, 2012;
33 Nelson, Rosella, Mahant, & Guttmann, 2016; Tsukada, Imataka, Suzumura, & Arisaka, 2012).
34
35 Regional variations in screening and care for infants with T13 or T18 and differences in
36 public, parental, or professional perceptions pose ethical challenges for parents and
37 professionals when encountering a prenatal diagnosis. Cases of longer-term survival, reports
38 of increased median survival times associated with more interventions, and readily
39 accessible online patient support groups have influenced attitudes (Janvier et al., 2016;
40 Janvier et al., 2012; Kosho et al., 2013).
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3 This study has limitations concerning heterogeneity and completeness of the data received
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5 from various registers. The data received included both hospital and population-based
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7 registers, ~~as~~ the former ~~represents~~ representing a selected population whereas the latter
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9 ~~represents~~ representing the whole region. There was no information on mosaicism, which
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11 could have effect on survival figures, as individuals with ~~mosaicisms~~ of T13 and T18 have
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13 better survival chances (Wu et al., 2013). However, this study provides an invaluable global
14
15 perspective over the years on the prevalence, pregnancy outcomes and survival of live born
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17 infants with T13 and T18. ~~It~~ The prevalence and outcome results highlights the variation in
18
19 data collection and management practices in this condition across different regions.
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26 **Acknowledgement:**

27 Results from Slovakia originated in cooperation with National Health Information Center in
28 Bratislava.

29
30 The work conducted at the ECEMC group was supported by the Instituto de Salud Carlos III
31 (ISCIII, Ministry of Science, Innovation and Universities) of Spain, and the Fundación 1000
32 sobre Defectos Congénitos of Spain. Components of ECEMC's Peripheral Group are gratefully
33 acknowledged.
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37 **Conflict of interest:** None to declare
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9 **Figure legends:**

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11 Figure 1. Total prevalence data for Trisomy 13 (1974-2015) from all registers A) with complete data
12 on LB, SB and ETOPFA; B) with data only on LB and SB
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15 Figure 2. A) Pregnancy outcomes in all registers in Trisomy 13 between 1974-2015; B) Three-year
16 rolling averages for prevalence of Trisomy 13 in registers where ETOPFA is reported (2001-2012)
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19 Figure 3. Live birth prevalence in all registers in Trisomy 13 (1974-2015)

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21 Figure 4. Mortality in live births (Trisomy 13) A) One year follow-up data in all registers*; B) Five year
22 follow-up in registers where outcomes were known; C) First year mortality from figure 4B shown in
23 further detail (dotted line represent 95% CI)

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25 Figure 5. Total prevalence data for Trisomy 18 (1974-2015) from all registers A) with complete data
26 on LB, SB and ETOPFA; B) with data only on LB and SB
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29 Figure 6. A) Pregnancy outcomes in all registers in Trisomy 18 between 1974-2015; B) Three-year
30 rolling averages for prevalence of Trisomy 18 in registers where ETOPFA is reported (2002-2013)

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32 Figure 7. Live birth prevalence in all registers in Trisomy 18 (1974-2015)

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34 Figure 8. Mortality in live births (Trisomy 18) A) One year follow-up data in all registers*; B) Five year
35 follow-up in registers where outcomes were known; C) First year mortality from figure 8B shown in
36 further detail (dotted line represent 95% CI)
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