

eAppendix

eTable 1. Proportion of direct mortality (due to pathology) in selected scenarios (non-T babies)<sup>1</sup>.

% Frequency of factor			Preterm birth	Total mortality (per 1,000)		Indirect mortality (per 1,000)		% direct mortality (due to pathology)	
Factor 1 Shift: -50 dd OR=4	Factor 2 Shift: -35 dd OR=1.25	Factor 3 Shift: -50 dd OR=2 (1.15) <sup>2</sup>	%	Total	Preterm	Total	Preterm	of total mortality	of preterm mortality
0.0	0.0	0.0	1.8	0.35	0.63				
0.6	0.0	0.0	2.4	0.40	2.72	0.36	1.03	9.3	62.1
0.0	4.0	0.0	5.4	0.38	1.03	0.38	0.92	1.6	10.7
0.0	0.0	0.6	2.4	0.43	4.01	0.36	1.03	15.3	74.4
0.6	4.0	0.0	6.0	0.46	2.21	0.39	1.12	13.9	49.2
0.0	4.0	0.6	6.0	0.48	2.60	0.39	1.12	18.0	56.8
0.6	4.0	0.6	6.5	0.56	3.64	0.41	1.32	26.5	63.8
0.3	0.0	0.0	2.1	0.38	1.84	0.36	0.86	4.9	53.3
0.0	0.0	0.3	2.1	0.39	2.58	0.36	0.86	8.4	66.8
0.3	4.0	0.0	5.7	0.42	1.69	0.39	1.03	8.7	39.1
0.0	4.0	0.3	5.7	0.43	1.89	0.39	1.03	11.1	45.7
0.3	4.0	0.3	6.0	0.47	2.45	0.39	1.13	16.3	53.8
0.0	8.0	0.0	9.0	0.42	1.19	0.40	0.97	4.7	18.2
0.6	8.0	0.0	9.5	0.51	2.09	0.42	1.15	17.5	45.2
0.0	8.0	0.6	9.5	0.53	2.27	0.42	1.15	20.1	49.5
0.6	8.0	0.6	10.1	0.63	3.16	0.45	1.32	29.3	58.3

<sup>1</sup>The estimates in the table are based on mortality rates calculated at the mid-point of each gestational week in the interval 24.5-45.5. The proportion of preterm birth is estimated based on the cumulative proportion of babies born from 24.0 to 37.0 weeks.

<sup>2</sup>The quantity in parenthesis reflects by how much the OR increases at each additional week that the fetus remains *in utero*.

eTable 2. Proportion of direct mortality (due to pathology) in selected scenarios (non-T babies)<sup>1</sup>.

% Frequency of factor			Preterm birth	Total mortality (per 1,000)		Indirect mortality (per 1,000)		% direct mortality (due to pathology)	
Factor 1 Shift: -60 dd OR=8	Factor 2 Shift: -50 dd OR=1.5	Factor 3 Shift: -60 dd OR=4 (1.3) <sup>2</sup>	%	Total	Preterm	Total	Preterm	of total mortality	of preterm mortality
0.0	0.0	0.0	1.8	0.35	0.63				
0.6	0.0	0.0	2.4	0.52	8.37	0.37	1.48	28.8	82.3
0.0	4.0	0.0	5.7	0.46	2.43	0.42	1.68	9.0	30.9
0.0	0.0	0.6	2.4	0.85	23.04	0.37	1.48	55.9	93.6
0.6	4.0	0.0	6.3	0.70	6.06	0.45	2.06	35.0	66.0
0.0	4.0	0.6	6.3	0.99	10.93	0.45	2.06	54.4	81.1
0.6	4.0	0.6	6.8	1.23	13.58	0.48	2.39	60.6	82.4
0.3	0.0	0.0	2.1	0.44	5.10	0.36	1.12	17.2	78.0
0.0	0.0	0.3	2.1	0.60	13.58	0.36	1.12	39.4	91.7
0.3	4.0	0.0	6.0	0.58	4.34	0.44	1.88	24.6	56.6
0.0	4.0	0.3	6.0	0.73	6.89	0.44	1.88	39.9	72.7
0.3	4.0	0.3	6.3	0.84	8.50	0.45	2.07	46.4	75.7
0.0	8.0	0.0	9.6	0.57	2.74	0.49	1.86	14.5	32.1
0.6	8.0	0.0	10.2	0.87	5.56	0.53	2.19	38.7	60.6
0.0	8.0	0.6	10.2	1.14	8.27	0.53	2.19	53.3	73.5
0.6	8.0	0.6	10.7	1.43	10.68	0.57	2.49	60.0	76.7

<sup>1</sup>The estimates in the table are based on mortality rates calculated at the mid-point of each gestational week in the interval 24.5-45.5. The proportion of preterm birth is estimated based on the cumulative proportion of babies born from 24.0 to 37.0 weeks.

<sup>2</sup>The quantity in parenthesis reflects by how much the OR increases at each additional week that the fetus remains *in utero*.

Full explanation of Table 2.

For any given non-T baby, there are four reasons for being born before day 280: (i) it was the baby's target gestation, (ii) the baby had Factor 2, (iii) the baby had Factor 3, or (iv) the baby had both Factors 2 and 3. Although babies exposed to T would never be born at their original target (because T reduced their target gestation by 20 days), they would also have four possible combinations of factors responsible for a short gestation: (i) T only, (ii) T and Factor 2, (iii) T and Factor 3, or (iv) T, Factor 2, and Factor 3.

Each of the above combinations has a different probability of occurrence, depending on the week of gestation at which the baby is born. Each combination is also associated with a different mortality risk (depending on both the time of birth and the effect on mortality of the factors causing the early birth). Table 3 (paper) shows the mixture of babies (and their risk of death) associated with each combination at three times of birth: day 189, 238, and 266 .

(Calculations are explained in the next section). The probability of having a target gestation of 189 days is near zero for both non-T and T babies. Therefore, all non-T and T babies born at 189 days have pathology as the reason of their early birth. However, while virtually all non-T babies at 189 days have both pathological factors, only 11% of T babies have both and 8% of T babies have only Factor 2 (which confers the least risk). This different mixture results in the OR of mortality due to T to be only 1.09 compared with non-T babies on day 189 (despite the fact that the "true" OR of mortality for T babies is 1.7 at all weeks).

Among births on day 238, almost all non-T babies are affected by either Factor 2 or 3 (12% have Factor 3, which at this point confers an OR of 55). Conversely, only 17% of T babies have either factor – most are born at 238 days only because of T – and very few have Factor 3. At day 238 the observed OR of mortality for T babies compared with non-T babies is 0.27 ,

reflecting the high prevalence of severe pathology (Factor 3) among non-T babies. At 38 weeks, virtually no baby has either factor (almost all those with a pathologic condition have been born by this point). The OR due to T is now 1.67 --very close to the true OR of 1.7.

Calculations behind the results in Table 3.

We illustrate the calculations behind Table 3 by focusing on babies born at 238 days of gestation (appendix table). For each combination of factors, we calculated the gestational age the babies would have had if they had not had T, Factor 2 (f2) or Factor 3 (f3). For example, a non-T baby with only Factor 3 would have had a gestational age 50 days longer, i.e., 288. A T baby with Factor 3 would have had a target gestation of 308 days (238+20+50), had it not had T and Factor 3, and so on. (See 2<sup>nd</sup> column in the table).

The relative frequencies of each combination of Factors 2 and 3 are determined by the parameters of the model. Because we condition on T, the sum of the four probabilities will be 1 within each category (“p( f2, f3 | T)” in the table). For example, the probability of having neither Factor 2 or Factor 3 is  $(1-0.006)*(1-0.04)$ ; the probability of having only Factor 3 will be  $(0.006)*(1-0.04)$ , etc.

The probabilities of each of the eight categories of target gestational age depend on the normal distribution (“p(tGA | f2, f3, T)” in the table). Each of the target gestations has a different probability of occurring (as can be seen by the virtually nil probability of having a target gestation of 300 days or higher). The probabilities were calculated by taking the difference between the cumulative density functions at each interval (1 day=0.1 SD).

We multiplied  $p(f2, f3 | T)$  by  $p(tGA | f2, f3, T)$  to obtain the probability of each combination of f2, f3 and target gestation among non-T and T babies, respectively. In this case, the probabilities

are all close to 0, because virtually no baby, regardless of T, had a target gestation this short (4.2 SD below the mean). By dividing each row value by the sum of the four probabilities within the corresponding stratum of T, we obtain the composition of the four combinations of f2, f3 in babies born at 238 days of gestation (last column). We calculated the mortality of each group by using the relevant mortality rate (based on equation (1) in main text) and OR (gestational-age-specific in case of Factor 3, constant in case of Factor 2). Appendix table. Steps to calculate the composition of babies without and with T given birth at a specific gestation (238 days in the example). (Final calculations are shown in table 2).

	Factors	Target GA	p( f2, f3   T)	p(tGA   f2, f3, T)	p(tGA, f2, f3   T)	Interval composition
Non-T	No Factor 2 or 3	<b>238</b>	0.9542	0.00001	0.00000677	0.0048
	Only Factor 2	273	0.0398	0.03229	0.00124519	0.8848
	Only Factor 3	288	0.0058	0.02779	0.00015528	0.1103
	Factors 2 and 3	323	0.0002	0.00000	0.00000000	0.0000
T+	No Factor 2 or 3	258	0.9542	0.00396	0.00011338	0.8548
	Only Factor 2	293	0.0398	0.01604	0.00001914	0.1443
	Only Factor 3	308	0.0058	0.00069	0.00000012	0.0009
	Factors 2 and 3	343	0.0002	0.00000	0.00000000	0.0000