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COMMENTARY

The unattainable criteria for new infant vaccines

Christopher J. Gill[a,b], Lauren Hodsdon[a], Mathuram Santosham[c,d], and Katherine L. O'Brien[c,d]

[a]Department of Global Health, Boston University School of Public Health, Boston, MA, USA; [b]Center for Global Health and Development, Boston University, Boston, MA, USA; [c]International Vaccine Access Center (IVAC), Johns Hopkins School of Public Health, Baltimore, MD, USA; [d]Center for American Indian Health, Johns Hopkins School of Public Health, Baltimore, MD, USA

ABSTRACT

Background. In 2013, the US Advisory Committee on Immunization Practices (ACIP) opted against adding meningococcal vaccines to the infant schedule due to poor cost-effectiveness. This raises a policy question: if meningococcal disease is too rare to justify routine vaccination, are there other vaccine-preventable causes of US infant deaths that could be supported?

Methods. We tabulated US infant deaths from 2009–2013 using the CDC WONDER database. These causes of death were then categorized into one of 3 categories: 1) vaccine-preventable using currently available interventions; 2) potentially vaccine-preventable within the next 10 years; and 3) not preventable.

Results. From 19.8 million births (3.9 million/year), ~122,000 infants died (0.62%). Of these, 181 (0.15% of all deaths) were preventable using currently available vaccines, while an additional 779 were categorized as potentially preventable in the next 10 y. By exclusion, 121,040 (99.2%) were judged 'not vaccine-preventable'. Meningococcal deaths contributed at most 0.03% of all infant deaths, but accounted for 17–34% of current vaccine-preventable deaths.

Conclusions. The low number of vaccine-preventable deaths in the US makes it increasingly difficult to justify the introduction of any new infant vaccines.

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ACIP; cost-effectiveness; infant mortality; meningitis; meningococcal vaccine; vaccines

Introduction

Over the past 100 y immense progress has been made in lowering US infant mortality. In 1915 the infant mortality rate was ~100 infant deaths per 1,000 live births, while the most recent data from CDC has this rate at ~6 infant deaths per 1,000 live births.[1] While the US rate lags behind several other wealthy nations, it remains a significant accomplishment. It has also created a distinct dilemma: as we strive to continue lowering this rate, the cost of prevention per life saved has continued to rise exponentially, restricting new preventative measures from meeting the cost-effective requirements for implementation. Traditionally, one of our most cost effective tools for reducing infant mortality has been through vaccinations, but this may no longer be the case.

In 2011, Glaxo-Smith-Kline (GSK) licensed the first multivalent conjugated meningococcal vaccine shown to be safe and efficacious in infants as young as 2 months of age (Hib-MenC-MenY). In 2013 a conjugated quadrivalent vaccine (Men ACWY-CRM) was licensed for use in infants 2 months and older, and in 2015 a meningococcus serogroup B vaccine was licensed for use in adolescents in the US and for use in infants 2 months and older in the United Kingdom. What this meant is that for the first time in history, we had the capability to protect against all medically important meningococcal serogroups.

However, in 2013 the CDC's Advisory Committee on Immunization Practices (ACIP) opted not to issue a general recommendation to add multivalent meningococcal vaccines to the routine US infant vaccination schedule.[2] Instead, it issued a 'permissive recommendation' that meningococcal vaccines be offered to children with certain immunological deficits that placed them at increased individual risk of meningococcal disease.[3,4] Yet, most of infant meningococcal disease occurs sporadically among infants with no definable immunologic predispositions.[5] Focusing only on high risk infants, means that meningococcal vaccines will not be stocked by general pediatricians, will not be used routinely in the general population, and so are unlikely to achieve the scale required to achieve herd immunity and disease elimination.

An important factor influencing the ACIP's decision was the historically low incidence of meningococcal disease in the US across all age groups, such that infant vaccination would not be cost-effective under any realistic scenario.[5-7] While logical, the ACIP's decision highlighted a larger issue confronting the pediatric, public health, and health policy-making communities. Namely, should we continue to develop novel infant vaccines? Or have we reached saturation where interventions will only reach modest reductions in lives saved?

In this commentary, my colleagues and I sought to create numerical context around this issue using meningococcal

CONTACT Christopher J. Gill cgill@bu.edu Center for Global Health and Development, Boston University; Associate Professor, Department of Global Health, Boston University School of Public Health, 801 Massachusetts Avenue, Boston, MA USA.

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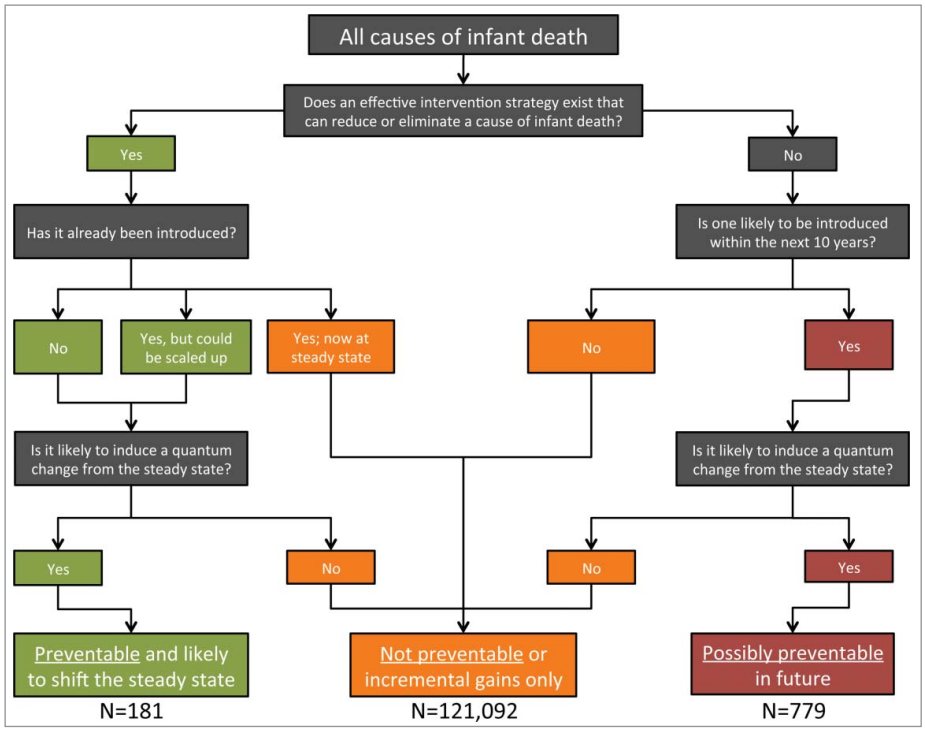

Figure 1. Flow diagram for categorizing causes of death as preventable, not preventable, or possibly preventable in the future. This flow diagram summarizes our reasoning process for triaging causes of death from CDC WONDER into each of the 3 categories. As noted elsewhere, there is subjectivity in this process. For example, one could debate the definition of 'quantum' vs. 'incremental' change, which could expand or contract the size of the fraction defined in each category to some degree. We accept those ambiguities, but contend that they do not negate our central thesis, which is that the days when big interventions can have big impacts at low costs are over.

deaths as a benchmark of comparison against other vaccine-preventable causes of infant death. We addressed the following questions:

1) From all US infant deaths, how many could reasonably be considered vaccine-preventable?
2) Of those, what proportion is represented by conditions for which we currently have a viable and potent vaccine that could be applied at scale (e.g., through a shift in policy) that would significantly alter the current 'steady-state'?
3) Is there a substantial residual burden of infant deaths that might be prevented through the introduction of new vaccines for which promising candidates in development currently exist?

Methods

To investigate causes of US infant deaths we used the CDC's WONDER (Wide-ranging Online Data for Epidemiologic Research) mortality database.[8] Given the impetus for this exercise, we limited this to infants < 1 y old, the period of peak meningococcal disease incidence, and the age range most directly affected by the ACIP's decision.[9] WONDER is a nationwide, open-access repository of causes of death in the US, based on death certificates with linkage to 4-digit ICD-10 codes. It also provides a birth cohort denominator. Since WONDER only tabulates deaths, we limited our analysis to mortality as the outcome of comparison, excluding non-fatal morbidity. We selected mortality *grouped by*- cause of death, *States*- All, *Urbanization*-All, *Ten-Year Age Groups*- < 1 year, *Gender*- All Genders, *Hispanic Origin*- All origins, *Race*- All Races, *Year/Month*- 2009 to 2013, *Weekday*- All, *Autopsy*- All, *Place of Death*- All, *Select cause of death*- ICD-10 Codes- All, *Rates Per*- 100,000. This data were accessed on Feb. 25th 2015. At that time, WONDER was complete through 2013. To obtain 5 y of data, we therefore combined years 2009–13.

From this list, we then sorted each cause of death into one of 3 categories: 1) Vaccine-Preventable Deaths; 2) Deaths that

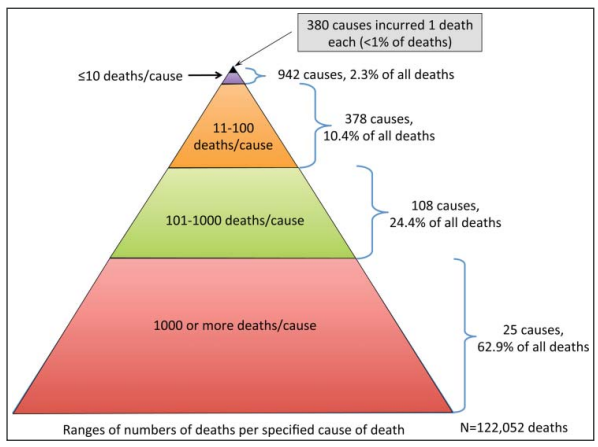

Figure 2. Summary of number of distribution of deaths among different causes of death among US infants < 1 y of age, 2009–13. This is a summary of deaths among US infants < 1 y of age from the CDC WONDER data set. It summarizes causes of death grouped by ranges of numbers of deaths within each category, contrasted against the total number of potential causes of death. For example, 'extreme prematurity', causing ~16,000 deaths, is included in the bottom most stratum of the pyramid, along with 24 other specified causes of death that each account for 1000 or more deaths in the set. To note, there is an inverse relationship between the numbers of causes of death and the numbers of deaths/cause. Stated another way, there are many potential causes of death that account for a very small number of actual deaths, and a very short list of conditions that account for the large majority of deaths.

Table 1. Top 50 causes of deaths in children < 1 y in the United States from 2009–13.

Cause of death	Deaths by cause	Cumulative deaths*	% of all deaths*	Cumulative % of all deaths*	Category of death	Preventable?	Comments /rationale
Extreme immaturity	15,995	15,995	13.11%	13.11%	Complications of prematurity	No, at steady-state	No effective way of preventing prematurity; efforts to mitigate impact have slowly improved over past few decades
Sudden infant death syndrome - SIDS	9,441	25,436	7.74%	20.84%	Other/ indeterminate	No, at steady-state	Current efforts to reduce SIDS through birth positioning already very effective; further gains possible but incremental
Other ill-defined and unspecified causes of mortality	5,018	30,454	4.11%	24.95%	Other/ indeterminate	Unknowable	Category is too broad
Other preterm infants	4,886	35,340	4.00%	28.95%	Complications of prematurity	Unknowable	Category is too broad
Newborn affected by premature rupture of membranes	3,911	39,251	3.20%	32.16%	Infection	Partially	GBS vaccine could reduce to some degree, though most infections in this category are NOT due to GBS
Accidental suffocation and strangulation in bed	3,460	42,711	2.83%	34.99%	Trauma	No, at steady-state	Current efforts to promote safe sleep behaviors already quite effective; further gains possible but would be incremental
Congenital malformation of heart, unspecified	2,811	45,522	2.30%	37.30%	Congenital or genetic conditions	No, at steady-state	Cannot be prevented; further improvement in prenatal diagnosis and treatment are likely but for incremental gain
Newborn affected by chorioamnionitis	2,433	47,955	1.99%	39.29%	Infection	Partially	GBS vaccine could reduce to some degree, though most infections in this category are NOT due to GBS
Respiratory distress syndrome of newborn	2,372	50,327	1.94%	41.23%	Perinatal complications	No, at steady-state	Current strategies for providing steroids to premature newborns already widely used
Edwards' syndrome, unspecified (Trisomy 18)	2,370	52,697	1.94%	43.18%	Congenital or genetic conditions	No	Cannot be prevented or cured
Bacterial sepsis of newborn, unspecified	2,338	55,035	1.92%	45.09%	Infection	Partially	Meningococcal and GBS vaccines might reduce this; Hib and pneumococcal vaccine uptake already very high.
Newborn affected by incompetent cervix	2,222	57,257	1.82%	46.91%	Perinatal complications	No, at steady-state	Management strategies currently exist; further improvements likely to be incremental
Neonatal cardiac dysrhythmia	2,133	59,390	1.75%	48.66%	Complications of prematurity	No, at steady-state	No effective way of preventing prematurity; efforts to mitigate impact have slowly improved over past few decades
Necrotizing enterocolitis of newborn	2,047	61,437	1.68%	50.34%	Complications of prematurity	No, at steady-state	No effective way of preventing prematurity; efforts to mitigate impact have slowly improved over past few decades
Newborn affected by other forms of placental separation and hemorrhage	1,918	63,355	1.57%	51.91%	Perinatal complications	No, at steady-state	No effective way of preventing prematurity; efforts to mitigate impact have slowly improved over past few decades
Neonatal cardiac failure	1,625	64,980	1.33%	53.24%	Complications of prematurity	No, at steady-state	No effective way of preventing prematurity; efforts to mitigate impact have slowly improved over past few decades
Anencephaly	1,511	66,491	1.24%	54.48%	Congenital or genetic conditions	No	Cannot be prevented or cured
Hypoplasia and dysplasia of lung	1,506	67,997	1.23%	55.71%	Complications of prematurity	No, at steady-state	No effective way of preventing prematurity; efforts to mitigate impact have slowly improved over past few decades
Other and unspecified gastroenteritis and colitis of infectious origin	1,306	69,303	1.07%	56.78%	Other/ indeterminate	No, at steady-state	No effective way of preventing prematurity; efforts to mitigate impact have slowly improved over past few decades
Primary atelectasis of newborn	1,301	70,604	1.07%	57.85%	Complications of prematurity	No, at steady-state	No effective way of preventing prematurity; efforts to mitigate impact have slowly improved over past few decades
Unspecified intraventricular (nontraumatic) hemorrhage of newborn	1,294	71,898	1.06%	58.91%	Complications of prematurity	No, at steady-state	No effective way of preventing prematurity; efforts to mitigate impact have slowly improved over past few decades

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Table 1. (*Continued*)

Cause of death	Deaths by cause	Cumulative deaths*	% of all deaths*	Cumulative % of all deaths*	Category of death	Preventable?	Comments /rationale
Hypoplastic left heart syndrome	1,292	73,190	1.06%	59.97%	Congenital or genetic conditions	No, at steady-state	Incremental improvements in prenatal diagnosis and treatment could slowly reduce this
Patau's syndrome, unspecified	1,251	74,441	1.02%	60.99%	Congenital or genetic conditions	No	Cannot be prevented or cured
Congenital diaphragmatic hernia	1,148	75,589	0.94%	61.93%	Congenital or genetic conditions	No, at steady-state	Incremental improvements in prenatal diagnosis and treatment could slowly reduce this
Multiple congenital malformations, not elsewhere classified	1,129	76,718	0.93%	62.86%	Congenital or genetic conditions	No, at steady-state	Can assume that some could be managed, some not; in any case, current deaths reflects steady-state capacity of system
Hydrops fetalis not due to hemolytic disease	887	77,605	0.73%	63.58%	Complication of pregnancy	No	Management strategies currently exist; further improvements likely to be incremental
Hypoxic ischemic encephalopathy of newborn	865	78,470	0.71%	64.29%	Perinatal complications	No, at steady-state	Management strategies currently exist; further improvements likely to be incremental
Birth asphyxia, unspecified	849	79,319	0.70%	64.99%	Perinatal complications	No, at steady-state	Management strategies currently exist; further improvements likely to be incremental
Congenital malformation, unspecified	808	80,127	0.66%	65.65%	Congenital or genetic conditions	Unknowable	Category is too broad
Unspecified pulmonary hemorrhage originating in the perinatal period	801	80,928	0.66%	66.31%	Complications of prematurity	No, at steady-state	No effective way of preventing prematurity; efforts to mitigate impact have slowly improved over past few decades
Newborn affected by multiple pregnancy	796	81,724	0.65%	66.96%	Complication of pregnancy	No, at steady-state	Management strategies currently exist; further improvements likely to be incremental
Assault by unspecified means	757	82,481	0.62%	67.58%	Trauma	No, at steady-state	Public awareness strategies currently exist; further improvements likely to be incremental
Unspecified threat to breathing	728	83,209	0.60%	68.18%	Other/ indeterminate	No, at steady-state	Management strategies currently exist; further improvements likely to be incremental
Other disorders of lung	686	83,895	0.56%	68.74%	Other/ indeterminate	Unknowable	Category is too broad
Intrauterine hypoxia, unspecified	663	84,558	0.54%	69.28%	Other/ indeterminate	No, at steady-state	Management strategies currently exist; further improvements likely to be incremental
Septicaemia, unspecified	633	85,191	0.52%	69.80%	Infection	Partially	Meningococcal and GBS vaccines might reduce this; Hib and pneumococcal vaccine uptake already very high.
Newborn affected by oligohydramnios	561	85,752	0.46%	70.26%	Perinatal complications	No, at steady-state	Incremental improvements in prenatal diagnosis and treatment could slowly reduce this
Renal agenesis, unspecified	528	86,280	0.43%	70.69%	Congenital or genetic conditions	No	Incremental improvements in prenatal diagnosis and treatment could slowly reduce this
Holoprosencephaly	485	86,765	0.40%	71.09%	Congenital or genetic conditions	No	Cannot be prevented or cured
Persistent fetal circulation	469	87,234	0.38%	71.47%	Perinatal complications	No, at steady-state	Incremental improvements in prenatal diagnosis and treatment could slowly reduce this
Polycystic kidney, unspecified	458	87,692	0.38%	71.85%	Congenital or genetic conditions	No	Incremental improvements in prenatal diagnosis and treatment could slowly reduce this
Perinatal intestinal perforation	428	88,120	0.35%	72.20%	Perinatal complications	No, at steady-state	No effective way of preventing prematurity; efforts to mitigate impact have slowly improved over past few decades
Intracranial (non-traumatic) hemorrhage of newborn, unspecified	419	88,539	0.34%	72.54%	Complications of prematurity	No, at steady-state	No effective way of preventing prematurity; efforts to mitigate impact have slowly improved over past few decades
Slow fetal growth, unspecified	407	88,946	0.33%	72.88%	Complication of pregnancy	No, at steady-state	Incremental improvements in prenatal diagnosis and treatment could slowly reduce this

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Table 1. (*Continued*)

Cause of death	Deaths by cause	Cumulative deaths*	% of all deaths*	Cumulative % of all deaths*	Category of death	Preventable?	Comments /rationale
Newborn affected by maternal hypertensive disorders	384	89,330	0.31%	73.19%	Complication of pregnancy	No, at steady-state	Incremental improvements in prenatal diagnosis and treatment could slowly reduce this
Other reduction deformities of brain	380	89,710	0.31%	73.50%	Congenital or genetic conditions	No	Only option would be prenatal screening and abortion
Bronchopulmonary dysplasia originating in the perinatal period	378	90,088	0.31%	73.81%	Complications of prematurity	No, at steady-state	No effective way of preventing prematurity; efforts to mitigate impact have slowly improved over past few decades
Down syndrome, unspecified	365	90,453	0.30%	74.11%	Congenital or genetic conditions	No	Cannot be prevented or cured
Potter's syndrome	360	90,813	0.29%	74.41%	Congenital or genetic conditions	No	Cannot be prevented or cured
Other secondary pulmonary hypertension	359	91,172	0.29%	74.70%	Complications of prematurity	No, at steady-state	No effective way of preventing prematurity; efforts to mitigate impact have slowly improved over past few decades

*Total US infant deaths 2009–2013 = 122,052
Abbreviations: CMV - Cytomegalovirus; GBS - Group B Streptococcus; HiB - *Hemophilus influenzae* Type B; SIDS - Sudden Infant Death Syndrome

might be Vaccine-Preventable in the next 10 y (Future preventable deaths); and 3) Not Preventable. This process was admittedly subjective, and it is likely that others might reach different conclusions (see Fig. 1).

'**Vaccine preventable deaths'** contain diseases for which an effective intervention already exists but is not being used (which would include meningitis vaccines), or for which expanded use could yield a substantial 'quantum' reduction in deaths. While we did not define 'quantum' specifically, it is reasonable to think of this as an intervention that could feasibly achieve a 90% reduction of deaths due to that cause.

For '**Future vaccine preventable'** deaths we included conditions with a reasonable expectation of an effective intervention within 10 y. This time interval was justified as reflecting the typical time to bring a promising new vaccine candidate from Phase 1 through licensure.

By contrast, deaths that were '**Not vaccine-preventable'** represent most of conditions. These are of 2 kinds. First, there are conditions for which there is no effective intervention. Second, there are many conditions with an effective intervention that is widely used already, which may include formally vaccine preventable conditions. Deaths from those conditions exist at a new steady-state that allows for incremental mortality reductions with time, but little expectation for a 'quantum' shift reduction. The concept of 'steady-state' is therefore essential to our reasoning. While counterintuitive, most vaccine-preventable diseases fail to meet our definition of 'preventable', because this quantum shift reduction has already occurred, creating a new (far lower) steady-state.

Results

Births, causes of death, and deaths attributed to specified causes

Between 2008–13 CDC WONDER listed 19.8 million live births in the US, or ~3.97 million/year. During this period, 122,052 infants died (~24,410 deaths/year), for a crude rate of 6.2 infant deaths/1000 live births. There were 1,456 causes of death. However, the first 25 conditions contributed 62.9% of total infant deaths. Conversely, 942 causes of death with <10 deaths/cause represented 65% of the 1,456 causes of death, but contributed only 2.3% of infant deaths (Fig. 2). Of these, 380 causes (26% of all causes but 0.3% of all deaths) incurred a single death each. Stated another way, despite a large number of potential causes of death, most infant deaths resulted from a few common causes.

Vaccine-preventable and non-preventable deaths

Table 1 summarizes the top 50 causes of US infant deaths, accounting for ~75% of deaths, none of which were vaccine preventable. The vast majority were due to prematurity, congenital conditions, intrauterine insults, and accidents/trauma. 'Extreme immaturity' was the leading cause with 15,995 deaths, or 13.1% of all deaths. However, the top 50 list included other specified complications of prematurity, bringing the total to 32,744 deaths, or 26.8% of all infant deaths. Infections accounted for 10.2% of infant deaths within the top 50 causes of death, and 7.6% of all infant deaths. However, none of these were pathogen-specific (as required for a vaccine) but rather syndromic conditions such as, "Newborn affected by chorioamnionitis," "Bacterial sepsis of the newborn," and "Septicaemia, unspecified." The first pathogen-specific cause of death (67th cause) was congenital herpes simplex virus with 266 deaths, or 0.22% of all deaths. There is no vaccine for HSV, and little expectation for one in the foreseeable future.

The first pathogen-specific cause of death with a promising vaccine candidate was Group B streptococcus (117th cause of death) with 125 deaths, or 0.1% of all deaths. "Septicaemia due to streptococcus, Group B" (226th) brought the total to 173 deaths, or 0.14% of all deaths (note that WONDER lists causes of death as reported, creating some degree of redundancy). Two other conditions, "Streptococcal meningitis" (86 deaths) and "Streptococcal septicemia, unspecified" (23 deaths) could

Table 2a. Infant deaths that are preventable now.

Cause of death	Number of deaths	% of all deaths	Comment
Whooping cough, unspecified	60	0.049%	Current uptake of infant pertussis vaccines is already very high and most deaths occur before effective immunization. Only realistic strategy would be to enhance uptake of maternal vaccination[1]
Influenza with other respiratory manifestations, virus not identified	36	0.029%	>50% of infant influenza deaths occur before 6 months of age, the earliest time that influenza vaccines become effective; the only realistic strategy would be to enhance uptake of maternal vaccination.[219]
Influenza with other respiratory manifestations, influenza virus identified	25	0.020%	Infant influenza vaccines are ineffective before 6 months of age; only realistic strategy would be to enhance uptake of maternal vaccination[192]
Meningococcemia, unspecified	22	0.018%	Effective vaccine licensed but only used in high-risk situations. Full protection would require combination of men ACWY and men B vaccines.[3]
Influenza with pneumonia, virus not identified	17	0.014%	Infant influenza vaccines ineffective before 6 months of age; only realistic strategy would be to enhance uptake of maternal vaccination.[2]
Whooping cough due to Bordetella pertussis	12	0.010%	Current uptake of infant pertussis vaccines is already very high and most deaths occur before effective immunization. Only realistic strategy would be to enhance uptake of maternal vaccination.[1]
Meningococcal meningitis	7	0.006%	Effective vaccine exists but only used in high-risk situations. Full protection would require combination of men ACWY and men B vaccines.
Meningococcal infection, unspecified	2	0.002%	Effective vaccine exists but only used in high-risk situations. Full protection would require combination of men ACWY and men B vaccines.
	181	**0.15%**	

add to total GBS deaths, depending on the proportion due to GBS specifically or to other streptococci (e.g., Group A streptococci, enterococcus, other Lancefield group streptococci, and viridans streptococci). It should be emphasized that these Group B Streptococcal deaths occur despite widespread utilization of prenatal maternal screening for vaginal colonization and the inclusion of prophylactic antibiotics as routine standard of care for colonized women. In other words, these deaths represent the residua of existing preventative programs, and thus represent the current steady-state, a steady-state that could be shifted with the introduction of GBS vaccines.

Current and possible future vaccine-preventable deaths

Table 2a summarizes the list of 181 deaths that we considered to be 'Vaccine-preventable'. Topping the list were pertussis and influenza. For pertussis, US infant DTaP uptake is already very high, and most deaths occur before vaccination or before an infant has achieved effective immunity.[10] Likewise, most influenza deaths occur in infants under 6 months of age, too young to mount an effective response to influenza vaccines.[11] Therefore, reductions in infant pertussis and influenza deaths would have to be achieved by increasing vaccination of pregnant women (as currently recommended by ACIP) to augment passive protection via maternal antibodies.

To note, on this short list of preventable diseases, meningococcal syndromes contributed 31 deaths, or 17.1% of currently vaccine-preventable deaths (Table 2b). However, this underestimates the burden of infant meningococcal disease since, as with GBS, meningococcal events are likely included in other syndromic causes of death, most notably meningitis. Including these raised the plausible tally of meningococcal deaths increased to 62 deaths (or roughly 15 deaths / year), accounting for 34.3% of vaccine-preventable deaths, but only 0.05% of all infant deaths.

To expand this further, Table 3 provides our list of vaccine-preventable deaths for which a promising candidate in development now exists. The leading causes were GBS (~300 deaths), CMV (138 deaths), and RSV (~318 deaths). The 300 deaths attributable to GBS is imprecise since it includes non-specific causes of death due to 'streptococci', plus other sepsis and meningitis syndromes. Similarly, the RSV total of 318 deaths is an overestimate since it includes syndromic deaths from bronchitis, tracheitis, and bronchiolitis that could be caused by other viruses. When limiting to

Table 2b. Possible additional meningococcal deaths.

Cause of death	Number of deaths	% plausibly from meningococcus	Additional deaths	Reference/s for assumption
Meningitis, unspecified	84	20%	17	[20,21]
Bacterial meningitis, unspecified	47	20%	9	[20,21]
Other bacterial meningitis	26	20%	5	[20,21]
Total	**215**		**31**	

Comment: Not included were various non-specific bacterial sepsis syndromes, '*Waterhouse-Friderichsen Syndrome*', '*Bacterial meningoencephalitis*', '*Meningomyelitis, not otherwise classified*', '*Disseminated intravascular coagulation*', and '*Other and unspecified adrenocortical insufficiency*'. While *N. meningitidis* is likely to be responsible for some fraction of these causes of death, assumptions about the responsible proportion were deemed too tenuous to justify their inclusion. The result is that these estimates for meningococcal deaths likely underestimate the true burden to some degree.

Notes: 1 In recent outbreaks in California, 10 infants died of pertussis. Only 24% had received any pertussis vaccines, and only a minority of their mothers had received Tdap during pregnancy.[22] 2. >50% of all infant influenza deaths occur between birth and 6 months. The per-month at risk mortality rate of influenza is 2.3 times higher among infants < 6 months vs. 6–23 months, with lower mortality rates in higher age groups.[23] 3. The highest incidence of meningococcal disease is among infants 0–5 months of age; 60% is due to serogroup B while most of the rest is due to serogroups C and Y. Therefore, prevention would require combined vaccination against B C and Y. Incidence is 2.6 cases/100,000 in infants < 5 months vs. 0.4/100,000 among adolescents and young adults.[24]

Table 3. Infant deaths possibly preventable within the next 10 y.

Cause of death	Number of deaths	% of all deaths	Comment
Sepsis of newborn due to streptococcus, group B	125	0.102%	Efficacy of GBS vaccine currently uncertain
Congenital cytomegalovirus infection	102	0.084%	Efficacy of CMV vaccine currently uncertain
Streptococcal meningitis	86	0.070%	Would not prevent deaths due to pneumococci, enterococci, Group A streptococci or other Lancefield groupings of streptococci
Acute bronchiolitis, unspecified	82	0.067%	Assumes most of these are in fact due to respiratory syncytial virus
Bronchitis, not specified as acute or chronic	61	0.050%	Assumes most of these are in fact due to respiratory syncytial virus
Septicaemia due to streptococcus, group B	48	0.039%	Efficacy of GBS vaccine currently uncertain
Acute bronchitis, unspecified	37	0.030%	Assumes most of these are in fact due to respiratory syncytial virus
Acute bronchiolitis due to respiratory syncytial virus	32	0.026%	Efficacy of RSV vaccine uncertain; enhanced uptake of RSV specific immunoglobulin could also reduce deaths
Respiratory syncytial virus pneumonia	31	0.025%	Efficacy of RSV vaccine uncertain; enhanced uptake of RSV specific immunoglobulin could also reduce deaths
Acute upper respiratory infection, unspecified	25	0.020%	Efficacy of RSV vaccine uncertain; enhanced uptake of RSV specific immunoglobulin could also reduce deaths
Streptococcal septicemia, unspecified	23	0.019%	Would not prevent deaths due to pneumococci, enterococci, Group A streptococci or other Lancefield groupings of streptococci
Acute tracheitis	23	0.019%	Assumes most of these are in fact due to respiratory syncytial virus
Influenza due to identified avian influenza virus	23	0.019%	Infant influenza vaccines ineffective before 6 months of age; only realistic strategy would be to enhance uptake of maternal vaccination; currently there is no vaccine specifically targeting avian flu
Cytomegaloviral disease, unspecified	21	0.017%	Efficacy of CMV vaccine currently uncertain
Streptococcal infection, unspecified	18	0.015%	Would not prevent deaths due to pneumococci, enterococci, Group A streptococci or other Lancefield groupings of streptococci
Cytomegaloviral pneumonitis	15	0.012%	Efficacy of CMV vaccine currently uncertain
Acute bronchitis due to other specified organisms	15	0.012%	Assumes most of these are in fact due to respiratory syncytial virus
Acute bronchiolitis due to other specified organisms	12	0.010%	Assumes most of these are in fact due to respiratory syncytial virus
Totals	**779**	**0.64%**	

Abbreviations: CMV - Cytomegalovirus; GBS - Group B Streptococcus; RSV - Respiratory Syncytial Virus

causes of death where the pathogen was specifically named, GBS fell to 173 deaths, CMV remained at 138 deaths, and RSV fell to 63 deaths.

Discussion

In summary, from ~19.8 million births over a 5-year period and ~122,000 deaths (0.62% of births), 181 (< 0.001% of births) could be avoided by currently available vaccines (assuming shifts in policy to promote their use), and an additional 779 (0.004% of births) might be preventable in the future assuming successful outcomes for the ongoing clinical development of GBS, RSV and CMV vaccines. Relative to the size of the birth cohort or even to the total number of infant deaths, the numbers of present and future vaccine-preventable deaths are almost immeasurably few (Fig. 3). Yet as a proportion of current vaccine-preventable deaths, meningococcal disease is number 3 on a short list: 17% under the most conservative assumptions, and plausibly a third of all vaccine-preventable infant deaths. How one views these numbers thus depends on one's goals. If this is to substantially reduce overall infant mortality rates, then none of these vaccines will have a measurable effect: even if all were combined, total US infant mortality would fall by less than half of one percent. But If our goal is to reduce the number of preventable deaths, a much smaller category, then the case for these vaccines becomes far more attractive. Stated another way, the choice of denominator really matters.

We make the following observations:

First, in the US, we have been extremely successful at managing the complications of prematurity, identifying and managing critical birth defects, minimizing complications of labor and delivery, preventing sudden infant death syndrome (SIDS), promoting car seats, and eliminating many of the leading infectious disease causes of infant mortality. Our infant mortality rate of ~6/1000 live births lags somewhat behind the best performing nations (currently led by Monaco, at 1.8 deaths/1000 live births), but is far far better than typical rates in developing countries, such as Zambia and Mali, where infant mortality rates are ~40/1000 and ~100/1000 live births,

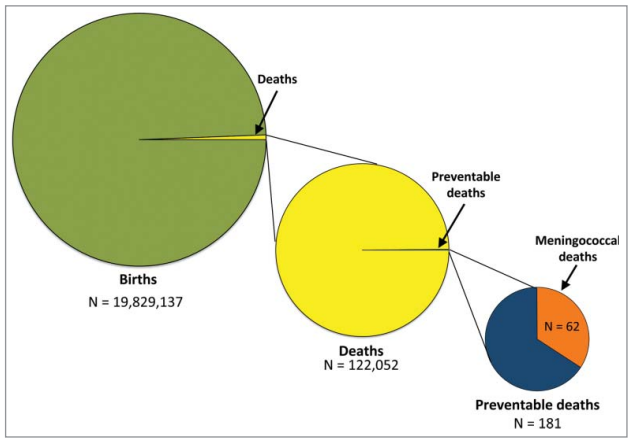

Figure 3. Comparison of the relative numbers of births, deaths, preventable deaths, and meningococcal deaths among US infants < 1 y of age, 2009–13. These pie diagrams depict the problem of which denominator to consider in estimating the relative benefits of hypothetical health interventions. To note, very few children die, and of those deaths, preventable deaths are an almost immeasurably small fraction of a fraction. As a proportion of the size of the birth cohort, any intervention one could name would exert a negligible impact. Even using the total number of deaths as the reference point is rigged against showing population level impact. In our view, neither denominator is meaningful when discussing strategies for reducing infant mortality. We argue that the relevant scale for these discussions must lie within the context of preventable deaths, a number that surely could be debated, but will inevitably be a small number. Source: CDC-WONDER.

respectively.[12] Logically, our priority in the US should be narrowing the infant mortality gap between us and Monaco. But even though this gap is small in absolute terms, narrowing it will be neither easy nor cheap.

Second, by definition, this low rate of infant mortality in the US had to have been achieved through the successful prevention of most of preventable deaths. The result is that the epidemiology of US infant mortality bears no resemblance to that of Zambia or Mali, where simple interventions can still yield large gains.

Third, by implication, the days when we could expect to see significant reductions in infant mortality for relatively modest investments of resources are over. The relationship between further investments in public health and further reductions in infant mortality generally has become asymptotic.

The implications of this 'new normal' are profound from a public health and ethical standpoint. For one, it means that traditional standards for cost-effectiveness are going to be challenging or impossible to meet for any new intervention. The licensure of prior conjugate vaccines provides an illustrative history of this shift. Prior to the introduction of conjugated vaccines against Haemophilus influenzae serotype b (Hib), ~20,000 cases occurred annually causing many deaths and severe sequellae.[13] The Hib vaccine was inexpensive, had minimal side effects, and was cost-saving to the health care system.[14] Prior to the introduction of PCVs, invasive pneumococcal disease afflicted ~4,000 US children/year.[15] But the vaccine, while highly effective, is technically complex and expensive to manufacture - especially when expanded from 7 to 10 or 13 serotypes. Yet the vaccine still proved cost-effective, especially when factoring in herd immunity.[16] Meningococcal disease is 10-fold less common than Hib or pneumococcal disease and vaccinating the infant birth cohort against Men ACWY and B will never be cost effective based on current thresholds, let alone cost saving.

It is true that the value of a vaccine is measured not merely in the numbers of deaths it prevents, but also in terms of the non-fatal morbidity it averts, the economic costs directly incurred in caring for the sick individual in the short or long-term, or the indirect costs to society, such as lost wages by care givers. And, in the case of meningococcus, there is a substantial cost due to the social disruptions that often follow from outbreaks. Perhaps RSV, being so common if less often mortal on a per case basis, might present a stronger rationale? Nonetheless, the bottom line of our analysis remains clear: if our goal is to reduce infant deaths in this country, then the options are now extremely limited, and we need to confront that reality with dispassion.

So, where does this leave us? We believe that our success in reducing infant mortality in the US has brought us to an ethical fork in the road. On the one hand, we could decide that we have done about as well as we can hope to do in reducing infant mortality, and that further investments to eliminate additional categories of deaths are unnecessary and unjustified. Following this logic, we would content ourselves with incrementalism. Alternatively, we could recognize the implications of the new normal, and continue to strive to identify new interventions capable of eliminating or significantly reducing specific causes of death, even if doing so demands ever diminishing yields on investment.

First and foremost, it feels urgent that the public health community engage in a wider discussion about the status quo and its implications, and what our goals can realistically be. That the US has reached a stage where infant mortality is extremely low forces us to think beyond cost-effectiveness and consider the death and suffering that can be averted in absolute terms - even if that comes at a high cost. Yet we acknowledge that at some point it will simply be too expensive to keep adding on new increasingly expensive interventions/treatments of an ever-diminishing yield; a break point must exist that reflects our values and our resources. Currently we have no consistent standards that define where this point lies. Identifying this must start by addressing this issue frankly and engaging in an open, transparent and sustained debate across a broad range of stakeholders, including pediatricians, patient groups, and policy makers.

Second, from this debate, we should strive to agree upon a set of common parameters to guide these kinds of decisions, and a framework for deciding for what qualifies as an intervention that is worth investing in. And we should then hold all prevention and treatment interventions to those same standards. One such tool should of course be cost-effectiveness. Traditionally, the US has set its "willingness to pay" threshold at $50,000 per quality adjusted life year (QALY) saved, though $100,000 per QALY has become increasingly common in recent years. Regardless of the number one choses, this does a dichotomous disservice by trying to parse the world of interventions around a threshold that is arbitrary. Editorializing on this conundrum, economists Neumann, Cohen and Weinstein wrote, "*Searching for a single benchmark is at best a quixotic exercise because there is no threshold that is appropriate in all decision contexts.*"[17]

Third, we must recognize that these thresholds are not absolute, but rather exist in some larger context that balancers social expectations, social desirability, and societal capacity, all of which can be expected to evolve with time. This means that a policy that may seem unaffordable today, could become a priority as expectations and resources shift. This concept was summarized beautifully by Geoffrey Vickers in his seminal essay on prioritizing actions in public health, *"I believe that the history of public health might well be written as a record of successful re-definings of the unacceptable."*[18]

Disclosure of potential conflicts of interest

Dr. Gill served as the clinical director for the Men ACWY vaccine program at Novartis Vaccines and Diagnostics from July 2008 to December 2010. However, he holds no stocks in Novartis, and has received no speaker, consultation, or promotional fees of any kind from Novartis or any other pharmaceutical company. He currently serves on a data safety monitoring board for Takeda vaccines overseeing the safety of a Norovirus candidate vaccine. The views expressed here are his own and not those of Novartis or any other company. The other authors have no conflicts to disclose.

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