Global Distribution of *Campylobacter jejuni* Penner Serotypes: A Systematic Review

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**Abstract**

Penner serotyping has been the principal method for differentiating Campylobacter isolates since its inception. Campylobacter capsule polysaccharide (CPS), the principal serodeterminant on which Penner serotyping is based, is presently of interest as a vaccine component. To determine the required valency of an effective CPS-based vaccine, a comprehensive understanding of CPS distribution is needed. Because of the association between Penner serotype and CPS, we conducted a systematic review to estimate the frequency and distribution of Penner serotypes associated with cases of Campylobacteriosis. In total, more than 21,000 sporadic cases of *C. jejuni* cases were identified for inclusion. While regional variation exists, distribution estimates indicate that eight serotypes accounted for more than half of all sporadic diarrheal cases globally and three serotypes (HS4 complex, HS2, and HS1/44) were dominant inter-regionally as well as globally. Furthermore, a total of 17 different serotypes reached a representation of 2% or greater in at least one of the five regions sampled. While this review is an important first step in defining CPS distribution, these results make it clear that significant gaps remain in our knowledge. Eliminating these gaps will be critical to future vaccine development efforts.

**Methods**

Relevant published data were identified from searches of PubMed for research articles containing the keyword “Campylobacter” and the term “Penner” or “serotype”. At the same time,
| First Author          | Country | Total | Year  | Duration | Age            | Catchment Area | Serotypes Tested |
|-----------------------|---------|-------|-------|----------|----------------|----------------|------------------|
| Karmali [13]          | Canada  | 285   | 1978  | 36       | Children 0 to >10 | Point          | 55               |
| Taylor [14]           | USA     | 46    | 1980  | 6        | Mixed          | Regional       | NS               |
| Skirrow [15]          | England | 3400  | 1981  | 132      | Mixed          | Country        | 43               |
| McMyne [16]           | Canada  | 153   | 1982  | NS       | NS             | Regional       | 55               |
| Lastovica [17]        | South Africa | 258 | 1982  | 6       | Children <10 | Point          | 60               |
| Georges-Courbot [18]  | CAR     | 94    | 1982  | 17       | Children <15  | Point          | 56               |
| Neogi [19]            | Bangladesh | 102 | 1983  | 12      | Mixed          | Point          | 42               |
| Patton [20]           | USA     | 149   | 1985  | NS       | NS             | Country        | 56               |
| Jones [21]            | Britain | 406   | 1985  | NS       | NS             | Unknown        | 32               |
| Sjogren [22]          | Sweden  | 29    | 1985  | 12       | Adults >15    | Point          | 23               |
| Sjogren [22]          | Mexico  | 130   | 1985  | 12       | Infants 0–5   | Point          | 23               |
| Nishimura [23]        | Japan   | 69    | 1985  | NS       | NS             | Unknown        | NS               |
| Chatzipanagiotou [24] | Greece  | 31    | 1987  | 12       | Children <14  | Point          | 25               |
| Albert [25]           | Australia | 108 | 1988  | 12      | Mixed          | Regional       | 66               |
| Albert [26]           | Australia | 12  | 1988  | 6       | Mixed          | Regional       | 66               |
| Sjogren [27]          | Kuwait  | 47    | 1989  | NS       | Mixed          | Point          | NS               |
| Zaman [28]            | Saudi Arabia | 46 | 1989  | 12      | Mixed          | Point          | NS               |
| Prasad [29]           | India   | 22    | 1989  | 132      | Mixed          | Regional       | 72               |
| Wareing [30]          | England | 754   | 1990  | 7        | NS             | Country        | 42               |
| Takahashi [31]        | Japan   | 455   | 1990  | 156      | NS             | Country        | 25               |
| Owen [32]             | UK      | 27    | 1992  | 12       | NS             | Country        | 45               |
| Asrat [33]            | Ethiopia | 35  | 1992  | 12      | Mixed          | Point          | 33               |
| Owen [34]             | England | 398   | 1993  | 12       | NS             | Country        | 47               |
| Marshall [35]         | England | 70    | 1994  | NS       | NS             | Point          | NS               |
| Gibson [36]           | UK      | 27    | 1994  | 2        | NS             | Country        | 45               |
| Nishimura [23]        | China   | 85    | 1994  | NS       | NS             | Regional       | NS               |
| Fang [37]             | Taiwan  | 27    | 1994  | 120      | Mixed          | Unknown        | 25               |
| Nielsen [38]          | Denmark | 136   | 1995  | 12       | NS             | Country        | 49               |
| Nielsen [39]          | Denmark | 42    | 1995  | 11       | NS             | Country        | 47               |
| Poly [5]              | Egypt   | 142   | 1995  | 43       | Infants 0–5   | Point          | 47               |
| Frost [40]            | Wales   | 2310  | 1996  | 12       | NS             | Country        | 66               |
| Hudson [41]           | New Zealand | 69 | 1996  | 7       | NS             | Point          | NS               |
| Strid [42]            | Denmark | 173   | 1996  | NS       | Mixed          | Country        | 47               |
| Petersen [43]         | Denmark | 42    | 1996  | 24       | NS             | Country        | 47               |
| Smith [44]            | Nigeria | 17    | 1997  | NS       | NS             | Point          | 64               |
| Sopwith [45]          | England | 2277  | 1997  | 24       | Mixed          | Regional       | NS               |
| McKay [46]            | Scotland | 3155 | 1998  | 12       | NS             | Country        | 66               |
| Moser [47]            | Germany | 201   | 1998  | 12       | NS             | Regional       | 9                |
| Chatzipanagiotou [24] | Greece  | 98    | 1998  | 24       | Children <14  | Point          | 25               |
| Poly [5]              | Thailand | 103 | 1998  | 72       | Adults >15    | Country        | 47               |
| Vierikko [48]         | Finland | 518   | 1999  | 3        | NS             | Country        | 25               |
| Saito [49]            | Japan   | 158   | 2000  | 36       | NS             | Regional       | 25               |
| Eyles [50]            | New Zealand | 54 | 2000  | 12       | Mixed          | Regional       | NS               |
| Ioannidis [51]        | Greece  | 207   | 2000  | 36       | NS             | Regional       | 25               |
| Gilpin [52]           | New Zealand | 66 | 2000  | 6       | NS             | Regional       | NS               |
| Nielsen [53]          | Denmark | 973   | 2001  | 12       | NS             | Regional       | 47               |
| Fussing [54]          | Denmark | 926   | 2001  | 13       | Mixed          | Regional       | 47               |
| Wierzb [55]           | Egypt   | 20    | 2001  | 30       | Mixed          | Point          | NS               |
| Oza [56]              | England | 414   | 2002  | NS       | NS             | Unknown        | 66               |
non-English publications, and review articles were excluded. The titles and abstracts of the identified articles were screened for relevance and evaluated independently by two of the study authors based on the availability of the article, and whether or not the article had previously unpublished, extractable data. Inclusion was limited to studies of natural sporadic Campylobacter jejuni infections in which human isolates were typed by the Penner-serotyping method. Research articles that reported data on fewer than ten isolates, data from outbreaks, or data from collections of isolates with evidence of selection bias (i.e. studies examining isolates from Guillain-Barré Syndrome patients only) were excluded. No further exclusionary restrictions were applied, such as the makeup of the study population, the length of the observation period, or the publication date. Disagreements concerning serotype assignment were resolved through discussion amongst all study authors. Serotypes were tallied within each study, and their respective proportions were calculated. Pooled proportional estimates were computed across all studies and within studies grouped by region. The proportional estimates were used to compute the relative global proportions calculated for the 35 C. jejuni serotypes outlined above. C. coli serotypes, when reported, were not included in this analysis. Discrepancies concerning serotype assignment were resolved through discussion amongst all study authors. Serotypes were tallied within each study, and their respective proportions were calculated. Pooled proportional estimates were computed across all studies and within studies grouped by region. The proportional estimates were computed using the DerSimonian & Laird random effects model [10]. Strong evidence of heterogeneity existed across the studies for most of the serotypes examined, the exception being those rarely reported in the literature (HS22, HS29, HS32, HS33, HS35, HS38, HS40, HS41, HS42, HS45, HS46, HS51, HS53, HS55, HS57, HS60, HS62, and HS66). All statistical analyses were performed using Stata Version 12 (College Station, TX).

**Results**

A search of the PubMed database identified 596 research articles for possible inclusion. After removing the duplicates, 488 research articles remained for consideration. A review of the titles and abstracts excluded another 410 articles from consideration based on relevance to the topic of interest, leaving 78 studies to be assessed for eligibility for inclusion. The full text of each of the 78 articles was examined in more detail, and data from 54 studies were included for the purpose of this review. Five publications reported stratified data that are included as separate studies for the purpose of this review, bringing the total number of studies to 59 (See Table 1 and Supplementary Figure S1).

In total, the studies were published between 1982 and 2011, reported data on 21,394 individual C. jejuni isolates from sporadic diarrhea cases identified; NC total number of isolates analyzed; NT year specimen collection initiated; NS when the year in which specimen collection began was not specified, publication year used; NT duration length of specimen collection period in months; NS age in years, “Mixed” indicates specimens collected from both children and adults; NT catchment size of the collection area, Point = a single collection point (e.g. single hospital or clinic); Regional = catchment indicates the size of the collection area; Mixed = a single collection point (e.g. single hospital or clinic); AGE = country from which sporadic diarrhea cases were identified; Total = total number of isolates analyzed; Year = year specimen collection initiated; Duration = length of specimen collection period in months; Age = age in years, “Mixed” indicates specimens collected from both children and adults; Catchment area = size of the collection area, Point = a single collection point (e.g. single hospital or clinic); Regional = catchment indicates the size of the collection area; Mixed = a single collection point (e.g. single hospital or clinic); **Table 1.**

| First Author | Country | Total | Year | Duration | Age | Catchment Area | Serotypes Tested |
|--------------|---------|-------|------|----------|-----|----------------|------------------|
| Cornelius [57] | New Zealand | 106 | 2002 | 2 | NS | Point | NS |
| Gilpin [58] | New Zealand | 168 | 2002 | 6 | NS | Regional | 43 |
| Schonberg-Norro [59] | Finland | 114 | 2002 | 3 | NS | Country | 25 |
| Sonnevend [60] | UAE | 41 | 2002 | 24 | NS | Point | 25 |
| Nakari [61] | Finland | 622 | 2002 | 48 | Mixed | Country | 25 |
| Nakari [61] | Finland | 785 | 2002 | 48 | Mixed | Country | 25 |
| Miljkovic-Selimovic [62] | Serbia | 29 | 2003 | 21 | NS | Regional | NS |
| McTavish [63] | New Zealand | 112 | 2006 | NS | Mixed | Country | 43 |
| Islam [64] | Bangladesh | 31 | 2006 | NS | NS | Point | NS |
| Grozdanova [65] | Macedonia | 20 | 2008 | 11 | NS | Regional | 25 |

*Country = Country from which sporadic diarrhea cases were identified; Total = total number of isolates analyzed; Year = year specimen collection initiated; Duration = length of specimen collection period in months; Age = age in years, “Mixed” indicates specimens collected from both children and adults; Catchment area = size of the collection area; Point = a single collection point (e.g. single hospital or clinic); Regional = catchment indicates the size of the collection area; Mixed = a single collection point (e.g. single hospital or clinic). **Table 1.**
cases of enteric infection collected between 1978 to 2008 from 29 different countries (Table 1). Study size and duration varied considerably. The largest and smallest studies comprised 3,400 and 12 isolates, respectively (mean = 363), while the duration of the studies analyzed ranged from 13 years to 2 months. The included studies also varied in design (i.e. sampling methodology and the size of the catchment area) as well as in their target populations (i.e. age, traveler vs. resident populations). The number of serotypes screened for in each study also differed, ranging from nine to 72 serotypes (including serotypes for C. coli) (See Table 1).

Overall, the studies predominately sampled European populations. Nearly 85% (n = 18,184) of the isolates included in this analysis were from Europe, while 1,186 were from Asia, 763 were from North America, 695 were from the Oceanic Region, and 566 were from Africa (Figure 1). No studies examining South America were identified in the literature search.

Globally, eight serotypes (HS4 complex, HS2, HS1/44, HS11, HS5/31, HS8/17, HS6/7, and HS3) accounted for 50.4% of all

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**Figure 1.** Proportional representation of the three most dominant HS serotypes (HS4c, HS2, and HS1/44) by region. Lightly shaded areas represent the 33 (of 35) HS serotypes not indicated in color on the graph. Darkly shaded areas indicating those isolates not accounted for in the 35 HS serotypes examined were empirically derived by subtracting the sum of the percentages of the 35 serotypes from 100%. The darkly shaded area also includes non-typable isolates.

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**Table 2.** Global HS Serotypes with Proportional Estimates of 2% or Greater.

| Global (n = 21,394) | %  | lci | uci |
|--------------------|----|-----|-----|
| HS4c               | 15.3| 12.9| 17.6|
| HS2                | 13.5| 11.3| 15.8|
| HS1/44             | 8.2 | 7.1 | 9.3 |
| HS1                | 3.1 | 2.2 | 4.0 |
| HS5/31             | 2.9 | 2.2 | 3.5 |
| HS8/17             | 2.8 | 2.2 | 3.4 |
| HS6/7              | 2.4 | 1.8 | 3.1 |
| HS3                | 2.2 | 1.7 | 2.7 |

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isolates. The dominant serotypes were those of the HS4 complex (15.3%, CI: 12.9, 17.6), HS2 (13.5%, CI: 11.3, 15.8), and HS1/44 (8.2%, CI: 7.1, 9.3) (See Table 2). Combined, these three serotype categories accounted for nearly 40% of all isolates reported worldwide. HS4 complex, HS2, and HS1/44 were also the three serotypes with the greatest proportional representation across each of the five regions examined (Table 3 and Figure 1). Moreover, these three serotypes remained the most prevalent serotypes when the data were stratified by the economic status of the country in which the study was conducted (Tables 4).

Beyond the three most dominant serotypes, in all, 17 different serotypes reached a proportional representation of 2% or more in at least one of the five geographic regions considered (Table 5). Nine serotypes reached the 2% threshold in Africa, Asia, and Europe, accounting for 46.1%, 42%, and 58.2% of the total number of isolates in each region, respectively. Combined, these three serotype categories accounted for nearly 40% of all isolates reported worldwide. HS4 complex, HS2, and HS1/44 were also the three serotypes with the greatest proportional representation across each of the five regions examined (Table 3 and Figure 1). Moreover, these three serotypes remained the most prevalent serotypes when the data were stratified by the economic status of the country in which the study was conducted (Tables 4).

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### Table 3. HS Serotypes with Proportional Estimates of 2% or Greater by Region.

| Region       | %   | lci  | uci  |
|--------------|-----|------|------|
| Africa (n = 566) |  |      |      |
| HS4c         | 7.0 | 2.8  | 11.2 |
| HS1/44       | 6.8 | 2.8  | 10.8 |
| HS3          | 6.3 | 1.1  | 11.6 |
| HS2          | 6.2 | 2.1  | 10.3 |
| HS5/31       | 6.2 | 2.3  | 10   |
| HS23/36      | 4.2 | 2.3  | 6.1  |
| HS8/17       | 4.1 | 0.1  | 8.1  |
| HS53         | 3.3 | 0.2  | 6.4  |
| HS19         | 2.0 | 0.6  | 3.4  |
| Asia (n = 1,186) |  |      |      |
| HS2          | 11.5| 6.1  | 17   |
| HS4c         | 8.9 | 4.3  | 13.5 |
| HS1/44       | 4.2 | 1.9  | 6.5  |
| HS15         | 3.4 | 1.1  | 5.7  |
| HS19         | 3.1 | 0.9  | 5.4  |
| HS23/36      | 3.0 | 0.9  | 5.0  |
| HS8/17       | 2.9 | 1.0  | 4.8  |
| HS3          | 2.6 | 1.1  | 4.2  |
| HS37         | 2.4 | 0.6  | 4.1  |
| Europe (n = 18,184) |  |      |      |
| HS4c         | 17.3| 14.6 | 20   |
| HS2          | 15.3| 12.1 | 18.5 |
| HS1/44       | 9.1 | 7.7  | 10.4 |
| HS11         | 4.0 | 2.8  | 5.2  |
| HS6/7        | 3.6 | 2.7  | 4.5  |
| HS5/31       | 2.6 | 1.9  | 3.4  |
| HS8/17       | 2.2 | 1.5  | 2.9  |
| HS12         | 2.1 | 1.4  | 2.8  |
| HS58         | 2.0 | 1.0  | 3.0  |
| N. America (n = 763) |  |      |      |
| HS4c         | 23.5| 15.3 | 31.7 |
| HS2          | 10.7| 4.3  | 17.1 |
| HS1/44       | 9.3 | 7.1  | 11.5 |
| HS5/31       | 6.8 | 3.0  | 10.5 |
| HS8/17       | 5.3 | 3.4  | 7.2  |
| HS3          | 4.9 | 1.8  | 8.1  |
| HS11         | 3.6 | 1.2  | 5.9  |
| HS21         | 2.5 | 0.8  | 4.2  |
| HS6/7        | 2.3 | 0.7  | 3.9  |
| HS18         | 2.1 | 0.8  | 3.4  |
| HS37         | 2.1 | 0.7  | 3.4  |
| Oceania (n = 695) |  |      |      |
| HS2          | 18.2| 7.9  | 28.5 |
| HS4c         | 17.4| 10.7 | 24.0 |
| HS1/44       | 10.5| 6.3  | 14.8 |
| HS8/17       | 8.8 | 3.5  | 14.1 |
| HS23/36      | 4.2 | 2.4  | 5.9  |

### Table 4. HS Serotypes with Proportional Estimates of 2% or Greater by Economic Development Status.

| Status       | %   | lci  | uci  |
|--------------|-----|------|------|
| Developed (n = 1,222) |  |      |      |
| HS4c         | 17.5| 15.2 | 19.8 |
| HS2          | 16.5| 13.8 | 19.1 |
| HS1/44       | 9.0 | 7.8  | 10.1 |
| HS11         | 3.5 | 2.4  | 4.5  |
| HS6/7        | 2.9 | 2.1  | 3.6  |
| HS8/17       | 2.8 | 2.1  | 3.4  |
| HS5/31       | 2.6 | 2.0  | 3.3  |
| HS3          | 2.1 | 1.6  | 2.6  |
| Developing (n = 20,172) |  |      |      |
| HS4c         | 8.2 | 4.8  | 11.5 |
| HS1/44       | 5.0 | 2.9  | 7.1  |
| HS2          | 5.0 | 2.8  | 7.3  |
| HS5/31       | 4.3 | 2.3  | 6.3  |
| HS3          | 3.7 | 1.7  | 5.7  |
| HS8/17       | 3.5 | 1.5  | 5.5  |
| HS23/36      | 3.3 | 1.5  | 5.1  |
| HS15         | 2.9 | 1.1  | 4.6  |
| HS53         | 2.9 | 1.0  | 4.8  |

Tables 2–4: HS serotypes with a proportional representation of 2% or greater, globally (Table 2), by Region (Table 3), and by Economic Status (Table 4). Proportional estimates (%) were computed using the DerSimonian & Laird random effects model and include the upper (uci) and lower (lci) 95% confidence intervals. Note: Isolates categorized as a cross-reactive pair HS serotype (e.g. HS1/44, HS5/31, HS6/7, HS8/17, and HS23/36) were originally reported as one of the two serotypes or as the paired serotype itself. Isolates categorized as HS4 complex (or HS4c) represent isolates reported as any combination of the following serotypes HS4/13/16/43/50/63/64/65. doi:10.1371/journal.pone.0067375.t004

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Isolates. The dominant serotypes were those of the HS4 complex (15.3%, CI: 12.9, 17.6), HS2 (13.5%, CI: 11.3, 15.8), and HS1/44 (8.2%, CI: 7.1, 9.3) (See Table 2). Combined, these three serotype categories accounted for nearly 40% of all isolates reported worldwide. HS4 complex, HS2, and HS1/44 were also the three serotypes with the greatest proportional representation across each of the five regions examined (Table 3 and Figure 1). Moreover, these three serotypes remained the most prevalent serotypes when the data were stratified by the economic status of the country in which the study was conducted (Tables 4).
Table 5. Comparison of HS Serotypes with Proportional Estimates by Region: Proportions that met or exceeded the 2% threshold are bolded and those that did not are indicated in italics.

|               | Global % | Africa % | Asia % | Europe % | N. America % | Oceania % |
|---------------|----------|----------|--------|----------|--------------|-----------|
| (n = 21,394)  | (n = 566) | (n = 1,186) | (n = 18,184) | (n = 763) | (n = 695)    |
| HS4c          | 15.3     | 7.0      | 8.9     | 17.3     | 23.5         | 17.4      |
| HS2           | 13.5     | 6.2      | 11.5    | 15.3     | 10.7         | 18.2      |
| HS1/44        | 8.2      | 6.8      | 4.2     | 9.1      | 9.3          | 10.5      |
| HS11          | 3.1      | 1.6      | 0.2     | 4.0      | 3.6          | 1.7       |
| HS5/31        | 2.9      | 6.2      | 1.8     | 2.6      | 6.8          | 1.5       |
| HS8/17        | 2.8      | 4.1      | 2.9     | 2.2      | 5.3          | 8.8       |
| HS6/7         | 2.4      | 1.2      | 0.7     | 3.6      | 2.3          | 0.6       |
| HS3           | 2.2      | 6.3      | 2.6     | 1.9      | 4.9          | 0.7       |
| HS37          | 1.8      | 0.9      | 2.4     | 1.8      | 2.1          | 1.8       |
| HS23/36       | 1.7      | 4.2      | 3.0     | 1.4      | 1.8          | 4.2       |
| HS21          | 1.6      | 0.5      | 0.6     | 1.8      | 2.5          | 1.1       |
| HS19          | 1.5      | 2.0      | 3.1     | 1.5      | 0.9          | 0.5       |
| HS12          | 1.3      | 1.0      | 0.0     | 2.1      | 0.5          | 0.7       |
| HS58          | 1.3      | 0.8      | 0.0     | 2.0      | 1.0          | 0.1       |
| HS15          | 1.1      | 1.4      | 3.4     | 1.2      | 0.9          | 0.4       |
| HS18          | 0.9      | 0.4      | 0.1     | 1.1      | 2.1          | 0.2       |
| HS53          | 0.7      | 3.3      | 1.2     | 0.7      | 0.6          | 0.1       |

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Discussion

Since Penner first introduced the method [2], serotyping has been an important means of characterizing Campylobacter isolates. Here, using existing data, we estimate the distribution of C. jejuni serotypes both globally and by geographic region. Estimates were derived from 59 published studies on more than 21,000 cases of sporadic diarrhea. Based on these estimates, eight serotypes account for half of all isolates globally and three serotypes in particular (HS4 complex, HS2, and HS1/44), were consistently represented across all regions.

Although this study is the first of its kind and a significant step forward in understanding the serotype distribution of C. jejuni infections, it is not without limitations. In fact, the estimates presented here are almost certainly imprecise. Data are sparse in every region of the world. No studies reporting extractable data were identified in South America and relatively few studies reported data from Africa and Asia, regions in which enteric infections contribute significantly to morbidity and mortality. The fact that some geographic regions are underrepresented may be partially due to the exclusion of non-English publications. However, the lack of data most probably reflects an absence of surveillance in these regions. With limited data from every region of the world, save Europe, the global estimates presented are biased towards those calculated in Europe. Even in Europe, from which 85% of the isolates in this study originated, there are insufficient data to draw conclusions regarding temporal changes in serotype distribution, geographic variation, and differences across demographic groups (e.g. travelers vs. non-travelers, or children vs. adults, etc.). The estimates presented here are also based on reports of sporadic cases of diarrhea. If an association between serotype and disease severity exists, selection bias has the potential to overestimate serotypes that result in manifest symptoms. Additionally, although a modest number of publications included in this review used a commercially available kit consisting of 25 antisera (Denka Seiken, Co), most studies relied upon custom reagents generated in-house or from another laboratory. The lack of standardized reagents calls into question the comparability of results across individual studies. Similarly, studies varied from one to the next with regards to which and how many serotypes were tested. These methodological differences undoubtedly influenced the estimates calculated here. Studies that did not screen a complete panel of antisera capable of detecting every serotype risked under-reporting certain serotypes, classifying them instead as non-typable. Finally, because C. jejuni is known to be subject to phase variation, assays such as Penner serotyping that depend upon the expression of CPS have the potential to underestimate the prevalence of any given Campylobacter serotype.

If current efforts to develop a CPS-based vaccine are to succeed, robust surveillance systems are needed to address substantial gaps in knowledge surrounding the geographic distribution and temporal stability of serotypes. Future surveillance methods should also aim to reveal demographic differences in serotype distribution (e.g. age, traveler vs. resident populations) and disease/serotype associations (e.g. severity of disease, risk of developing chronic long-term health outcomes such as reactive arthritis, Guillain-Barré syndrome, or gastrointestinal disorders). Combined with investigations into the immunogenic properties of the differing CPS types, addressing these fundamental surveillance-related questions will be important in determining the composition of a future vaccine with regards to valency. Furthermore, the need for surveillance is greatest in developing regions, where diarrheal disease is most prevalent and available data are lacking. Diarrheal episodes amongst children in the developing world are believed to cause millions of deaths annually [11] and, although the estimates are derived from a relatively small number of studies, the proportion of diarrheal cases attributable to Campylobacter infection is believed to be high, ranging between 5–20% of cases.
Given this high incidence rate, the potential benefit of a future vaccine is greatest in the developing world. However, realizing this potential will require a significant surveillance effort to inform the development of a multi-valent vaccine that is well-matched to CPS types circulating in these regions. Implementation of such a surveillance program will require a commitment of time and resources that has not been seen to date. Although Penner typing was once considered the gold standard in C. jejuni serotyping, its use has been declining in recent years and, today, the technique is routinely performed by only a small number of reference laboratories in North America and Europe. The limited and declining use of Penner typing is due in part to the complexity and cost of generating polyclonal rabbit sera to the 47 C. jejuni type strains, as well as to the emergence and value of other typing schemes such as Multi Locus Sequence Typing (MLST) and the ever-decreasing cost of direct sequencing. For a surveillance system to be implemented that is sufficiently large enough to address the outstanding questions of CPS distribution and disease association, alternative methodologies for determining the CPS type of C. jejuni isolates will almost certainly need to be employed. Such alternative methodologies will need to be cost-effective, efficient with respect to time, readily transferred to most any laboratory, and have high throughput capacity. Recently, our group offered a method that meets these criteria. Sequencing has revealed that each Penner serotype is unique with regards to the genomic structure of the cassette of genes involved in the biosynthesis of the serodeterminant CPS [5]. We have designed specific PCR primers that exploit these genomic differences and reproduce the original Penner serotypes. The published system covered 14 serotypes, and has recently been extended to 47 serotypes, (Poly et al. in preparation). Standardization and distribution of this CPS typing system offers one potential alternative method for large-scale surveillance. In addition to the already noted benefits this molecular typing system might offer, such a system may also reduce or eliminate the substantial number of non-typable isolates found in previous studies, as the described PCR-based typing system it is not sensitive to CPS expression. Regardless of which method is ultimately used, informed design of a CPS-based vaccine will require a substantial investment of resources to sustain the intensive surveillance needed to move beyond the incomplete and static picture that this review is able to offer.

Supporting Information

Figure S1 Flow diagram of articles search, reviewed, and included in the systematic review. (DOCX)

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Author Contributions

Conceived and designed the experiments: BP PG FP. Performed the experiments: BP FP. Analyzed the data: BP FP. Wrote the paper: BP PG FP.

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