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Review

Animal influenza in the Caribbean: a systematic review of research and surveillance

Influenza animal en el Caribe: revisión sistemática de investigación y vigilancia

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Pastor Alfonso*, **Carmen Laura Perera González**, **Haymee Canales Becerra**

Centro Nacional de Sanidad Agropecuaria (CENSA), OIE Collaborating Center for Reduction of the Risk of Disaster in Animal Health. San José de las Lajas, CP 32700, Mayabeque, Cuba.

ABSTRACT: Current influenza surveillance and pandemic mitigation strategies, addressing One Health from a global perspective, demand a broader geographic capacity for research and surveillance on animal influenza viruses (IVs). The aim of this work was to characterize the temporal and geographic shape of research and surveillance on animal IVs in the Caribbean region. A retrospective study, based on the PRISMA statement, was conducted to systematically review the peer reviewed articles on animal IVs generated in Caribbean countries from January 1950 to March 2019. References were obtained from PubMed Central and Sciendirect databases, whereas Academic Google and some animal disease databases were used as supplementary data sources. The selection process identified 32 articles or disease reports generated from 2007 to March 2019, which averaged 2.66/year. There was an overall trend of increased numbers of articles over time, although it varied among topics. The diagnosis embodied the majority of studies (14, 43.75 %) and the scattering by species showed a vast predominance of those targeting avian (wild bird and poultry) species with respect to swine and horses. The disease reports were restricted to avian influenza (AIV) in poultry with five notifications submitted by three different countries (Dominican Republic, Haiti and Belize), which were all due to an H5N2 low pathogenic (LP) AIV. This systematic review suggested the need of a further increase in scientific studies on animal influenza generated in the Caribbean based on risk assessment and networking through international collaboration.

Key words: One Health, influenza, surveillance, Caribbean.

RESUMEN: Las actuales estrategias de vigilancia de la influenza y de mitigación de pandemias, enfocadas desde la perspectiva de Una Salud, exigen una capacidad geográfica más amplia para la investigación y vigilancia de virus influenza en animales (VI). El objetivo de este trabajo fue caracterizar la distribución temporal y geográfica de las investigaciones y la vigilancia sobre VI en animales en la región del Caribe. Se realizó un estudio retrospectivo, basado en la declaración PRISMA para revisar sistemáticamente los artículos generados en países del Caribe desde enero de 1950 hasta marzo de 2019. Se obtuvieron referencias de las bases de datos PubMed Central y Sciendirect, mientras que Google Académico y algunas bases de datos de enfermedades animales se utilizaron como fuentes suplementarias de información. El proceso de selección identificó 32 artículos o informes de enfermedades generados entre 2007 y marzo de 2019, que promediaron 2,66/año. Hubo una tendencia general al crecimiento del número de artículos en el tiempo, aunque varió entre los temas. El diagnóstico representó la mayoría de los estudios (43,75 %) y la distribución por especies mostró predominio de aquellos dirigidos a aves (silvestres y de corral) con respecto a cerdos y caballos. Los informes de la enfermedad se restringieron al virus de la influenza aviar (VIA) en aves de corral con cinco notificaciones enviadas por tres países diferentes (República Dominicana, Haití y Belice), debidas a un VIA H5N2 de baja patogenicidad. Esta revisión sistemática sugirió la necesidad de estudios sobre la influenza animal en el Caribe basados en la evaluación de riesgos y la creación de redes a través de la colaboración internacional.

Palabras clave: Una Salud, influenza, vigilancia, Caribe.

*Corresponding author: *Pastor Alfonso*. E-mail: alfonso@censa.edu.cu

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INTRODUCTION

Influenza A viruses (IAVs) are among the most challenging viruses that threaten both human and animal health (1). From a One Health perspective, their capability to transmit from one species to another, causing multiple viral genome reassortments to occur is of major concern. The best studied pandemic IVs, in 1918, 1957, 1968, and 2009, ultimately acquired some or all of their gene segments from the avian IAV gene pool with swine origin genes in a second order (2,3). The last two decades have witnessed a growing list of avian influenza viruses (AIVs) that could infect humans with severe consequences (4), while the role of swine in interspecies transmission of IAVs continues to be of concern (5,6).

There are long-standing evidences that relate presumed equine influenza viruses (EIVs) to human epidemics or pandemics, but lacks confirmation by modern scientific methods (2). Current indications of zoonosis with EIVs mostly come from regions where humans still have close contact with horses (7). Other animals which are in close contact with humans such as dogs were not considered a natural host of IAVs until an H3N8 virus infected dogs through transmission from equine species. This occurrence furthered originated a unique dog stable lineage (8). Dogs can be also be infected by AIVs, which raises concern for public health (9,10).

The unpredictability of an influenza pandemic highlights the need for improved surveillance on animal IVs and for research to understand and manage the risk of spillover between animals and humans. While the world prepared to face a conceivable H5N1 avian-origin influenza Eurasian lineage pandemic, a H1N1 pandemic virus emerged from swine in North America. Information on the geographic variation of IV emergence risk and/or spillover, framed within concurrent surveillance efforts, is essential for the design of future influenza surveillance and pandemic mitigation strategies (11).

There is a unique article summarizing AIVs detections in domestic poultry in the Caribbean and other locations, which covered 2006 to 2008 and mainly focused on case description (12). An updated review of animal IV surveillance programs is needed to assess the capacity for detecting IVs with zoonotic potential. This would assist to determine the global need for increasing surveillance, which targets these viruses in relevant animal species (13,14). However, surveyed countries in this article revealed that in the Caribbean, only four out of 28 nations (14.29 %) provided data. Such disparity with regards to the overall coverage of the study (40,91 %), could be due to the fact that these countries were targeted by the Food and Agriculture Organization of the United Nations (FAO), which excluded small island states and overseas territories. Therefore, information on both research and surveillance of IAVs in the Caribbean was determined by regional capacity to perform the testing.

Several facts underline the importance of such data for the Caribbean countries that may contribute to the global body of knowledge. For this subregion several factors contribute to the risk for avian influenza with high impact (15,16). Moreover, swine, as other species of main concern for IAVs surveillance, account for important populations among some Caribbean countries (17) in which they constitute a main concern of local food security. Therefore, noteworthy levels of contact intensity among animal species and humans for IAVs infections could be present in this subregion. Additionally, either the frequency or intensity in which the Caribbean region is impacted by hurricanes might recurrently enhance the vulnerability of animal and human populations for higher risk of exposure to pathogens, including IAVs. Additionally, island territories face further challenges owing to their isolated geographies (18).

Systematic reviews on health-related issues are essential to determine trends or data collection needs, which provide evidence for policy makers to develop interventions toward risk reduction and management, which will build defensive capacities for the reduction in biological threats. In particular, within the Caribbean there are some regional organizations, including an Animal Health Network (CaribVET) (https://www.caribvet.net/) prone to addressing capacity building for resilience, among other topics that could improve outputs for a systematic review on animal influenza. A systematic review on animal IV research and surveillance was conducted across the Caribbean region based on the assumption that publication trends capture varying and evolving regional capacity on these topics. The aim of this work was to characterize temporal and geographic data and international research collaboration. We addressed the capability for research and surveillance on animal influenza in the Caribbean region.

METHOD

A prior protocol was accomplished, based on the PRISMA statement (19) to specify the search strategy, eligibility criteria, objectives, and the methods of this systematic review. The available scientific publications generated in Caribbean countries were searched, retrieved and analyzed for their content, quality and relevance. Additionally, animal disease web-based applications like WAHIS (http://www.oie.int/wahis_2/public/wahid.php/Wahidhome/Home) from the Organization for Animal Health (OIE), the FAO's Global Animal Disease Information System (http://empres-i.fao.org/eipws3g/) and GenBank (https://www.ncbi.nlm.nih.gov/genbank/) were used for screening records or reports related to animal influenza in the Caribbean and to supplement the scientific publication data.

Eligibility criteria

The retrospective study was conducted to review the articles on animal influenza in the Caribbean published from January 1950 to March 2019. This search focused on articles written in English, French, or Spanish. One reviewer screened the retrieved records to exclude those not matching through titles and if necessary, the abstract. In case of doubts, the consensus was reached by discussion between two review authors and if necessary, examining the full text publication of concern. Review articles were excluded, but after a carefully reading to assess if they contained information, which allowed tracing back some relevant articles potentially not identified through the search strategy.

The abstracts or articles were obtained from PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/) and Sciencedirect (https://www.sciencedirect.com/) databases, and Academic Google (https://scholar.google.com.cu/) was also used to judge the first 200 retrieved articles ordered by relevance. The descriptions used in the record retrieval process included the following terms: influenza, Caribbean and animals, combined under the following search strategies: 'influenza' AND 'animals' AND 'Caribbean' and 'influenza' AND 'Caribbean' AND ('swine' OR 'poultry' OR 'bird' OR 'equine'). A search was also carried out using the strategy: 'influenza' AND ('animals' OR 'swine' OR 'poultry' OR 'bird' OR 'equine').

The search strategy replaced the term Caribbean by the single countries/territories denomination such as: Anguilla, Antigua & Barbuda, The Bahamas, Barbados, Bermuda, Bonaire, British Virgin Islands, Cayman Islands, Cuba, Dominica, Dominican Republic, Grenada, Guadeloupe, Haiti, Jamaica, Martinique, Montserrat, Netherland Antilles (includes Aruba, Sint Maarten, Curacao), Puerto Rico, Saint Barthelemy, Saint Eustatius, Saint Kitts & Nevis, Saint Lucia, Saint Martin, Saint Vincent & the Grenadines, Trinidad & Tobago, Turks & Caicos Islands, and the US Virgin Islands. Denomination of group of islands or the vernacular name within a group were also used, namely Hispaniola, Jost Van Dyke, Leeward Islands, Saint Croix, Saint John, Tortola, Virgin Gorda, and Water Island. The remaining CARICOM member states (Belize, Guyana, Suriname, and French Guiana) were also included in the search. Thirty-two mainland or island countries/territories were considered as the Caribbean.

Inclusion and exclusion criteria

a. *Inclusion criteria:* Abstracts were included if they described:

b. data relating to animal influenza in animals or humans in any of the 32 detailed countries in the Caribbean,

c. data from surveys of animal influenza obtained using serological, virus isolation and nucleic acid detection,

d. proposal or development of any procedures applicable to the surveillance and control of animal influenza,

e. development or evaluation of surveillance systems, and
f. animal influenza vaccine development or evaluation.

a. *Exclusion criteria:* Abstracts were excluded if they
b. did not refer to original research data on animal influenza or
c. did not describe naturally occurring infections by animal influenza in the Caribbean, and
d. in case of similar results in more than one article the less comprehensive study was excluded

Data extraction and synthesis

The database was built in Zotero 5.0 (https://www.zotero.org/). Once the Digital Library was constructed and duplicate records removed, the titles and abstracts were analyzed and revised against the inclusion criteria to determine their relevance and suitability. The following data were extracted from the publications selected for inclusion of the author(s), year of publication, geographic location in which the study was conducted, and the design of the study. Other extracted data included were the subtypes, the animal species and the category tested.

The articles were classified according to their content in topics such as: 1) Diagnosis (virological, molecular or serological); 2) Proposal or development of any procedures applicable to the surveillance and control; 3) Development or evaluation of surveillance systems; 4) Surveillance studies on wild bird or poultry (commercial or backyard), and 5) Vaccine development or evaluation. For analysis of diagnosis, the serological approaches were considered separately, whereas viral isolation and identification, as well the nucleic acid detection were grouped under virological diagnosis. For surveillance studies involving more than one country, descriptive statistics consider the first author´s country/territory. A spreadsheet in Excel® (Microsoft, USA) was structured and the information entered according to the above-mentioned categories to process descriptive indicators of frequency distributions.

Social Network Analysis of collaboration

From the bibliometric database, information was extracted, including institutional names, number of authors, institutions and countries to carry out social network analysis (SNA) of collaboration. For each included paper, one author examined the data based on the full texts with information checked by a second author. A process of standardization was carried out to combine various institution or countries/territories. In the case of departments or branches attached to universities or Ministries of Agriculture, the affiliation was considered as an institution. A binary matrix of relationships between countries and institutions was constructed, considering only contacts (link or edges) involving at least one Caribbean country/territory. Data was imported to Gephi 0.9 program to construct, metric and visualize the network for collaboration to generate pertaining articles.

RESULTS

Search results

During the selection process, PMC yielded 8979 records, Sciendirect1094records, Google Scholar 200 results, and WAHIS 5 reports. A total of 10278 articles, of which 2598 were duplicates, left a total of 7680 reports. The study selection process was summarized in a flow diagram (Fig. 1). After the initial review of all studies by the first and last author and subsequent discussion, and the consensus of the remaining author, 6115 articles/records were discarded after screening the title and if necessary the abstract, while 1383articles/records were discarded as they did not meet the eligibility criteria. One hundred eighty-two publication articles from the electronic databases mentioned were eventually deemed potentially relevant studies for inclusion in this review and 32 were found to be pertinent and included after a full-text screening.

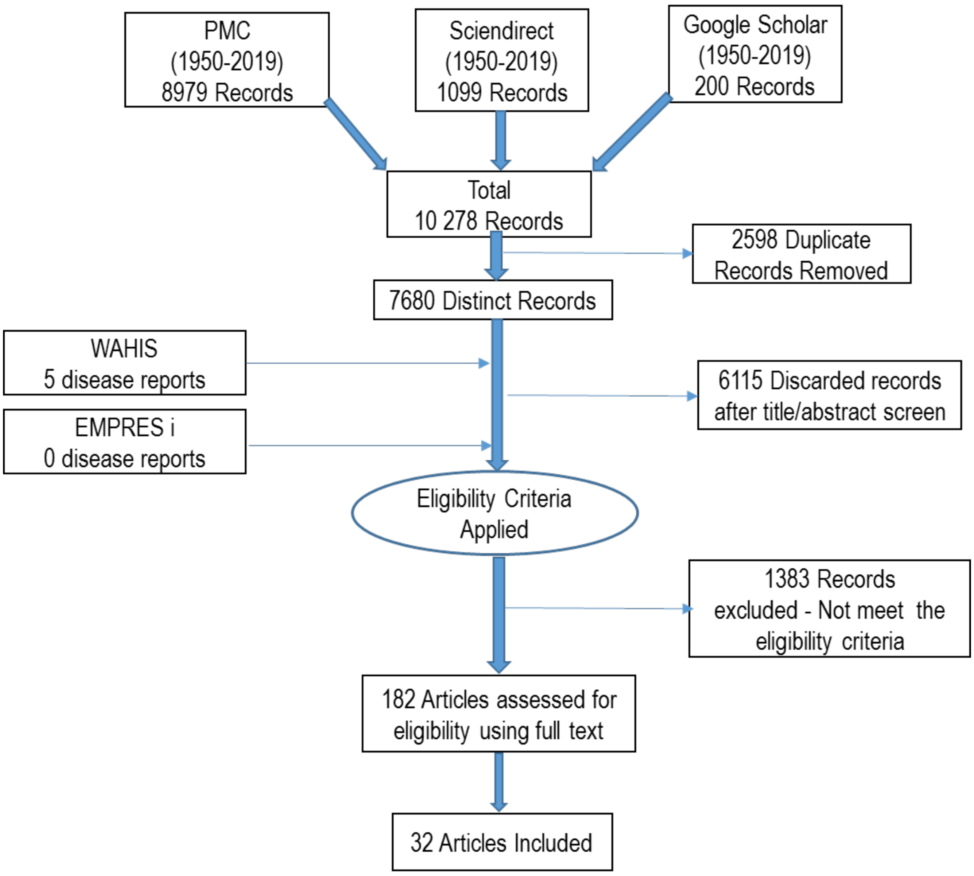

Figure 1. Flow chart documenting literature retrieval and criteria used to select articles for inclusion in the systematic review of peer reviewed original studies on animal influenza generated in the Caribbean. /*Diagrama de flujo de la recuperación de literatura y los criterios utilizados para seleccionar artículos para su inclusión en la revisión sistemática de estudios originales sobre la influenza animal generada en el Caribe, revisados por pares.*

Characterization of included studies or reports

During the retrieval of pertaining studies (2007- March 2019), 32 articles or reports generated in the Caribbean were identified (≈2.66/year). There was a ratio of 5.4 articles per disease report. The temporal distribution of studies (Fig. 2) showed a clear overall trend, which increased over time although it varied among topics. The largest amount of studies per year was six in 2018, the last entirely concluded year.

The 32 studies (articles/reports) occurred in six sections (Table 1). This distribution showed that the serological and virological diagnosis paired with each other (7, 21.87 %) and represented the largest number (14, 43.75 %) of studies within a particular topic followed by vaccine development (5, 15.62 %). Thereafter, the amount of studies on development of nucleic acid detection approaches (4, 12.5 %) equated to the OIE disease reports and were followed by the development or evaluation of surveillance systems (3, 9.37 %). Cuba was the only country that published studies on AIV vaccine development. Among these included the diagnostic tests used for vaccine evaluation.

The spatial distribution of data for swine and horses was narrow, with only 3 articles concerning swine in one country, whereas the other in horses was carried out in 3 Leeward Islands (St. Kit, Nevis, and Sint Eustatius). In contrast, the OIE animal influenza reports listed by species other than avian were absent, and no reports were retrieved through alternative disease information sources (http://empres-i.fao.org/eipws3g/).

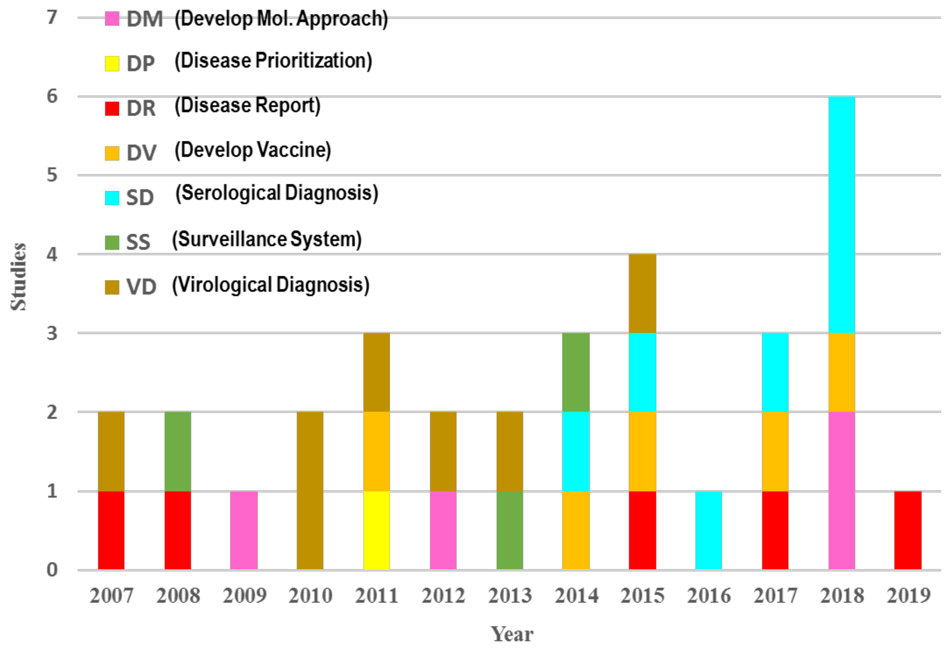

Figure 2. Temporal distribution of animal influenza studies generated in the Caribbean region. / *Distribución temporal de las publicaciones sobre influenza animal en el Caribe.*

The diagnosis, the most represented data, when scattered per species (Fig. 3) showed a vast predominance (almost two thirds) of studies targeted avian (wild bird or poultry) compared to swine and horses. However, within the studies on avian (15,16,24,25,26,27,28,35,36,45,49), the majority addressed poultry (commercial or backyard) from which 8 out of 10 were on commercially reared poultry.

The studies listed by the first author's affiliation were distributed in nine countries/ territories, highlighting the fact that two of them were found in OIE disease reports (25,26,27,28). The frequency of studies per country revealed that the greatest number corresponded to Cuba (15, 46.87 %), which coincided with a broadest thematic diversity. Cuba produced almost a fourfold number compared to Trinidad and Tobago, which was the second highest country (Fig. 4). Cuba was the most productive, even subtracting studies on vaccine development.

Excluding OIE diseases reports, only 7 out of 32 countries/territories provided articles. Among such countries/territories, Cuba, Trinidad and Tobago, Grenada, and Guadeloupe provided the largest number of articles, which accounted for 22 out of 27 (81.48 %).

Table 1. Studies on animal influenza generated in the Caribbean. /*Estudios sobre influenza animal generados en el Caribe.*

Thematic	No. of articles	References
Development of molecular approaches	4	13,20,21,22
Diseaseprioritization	1	23
Disease reports	5	24,25,26,27,28
Development of vaccines	5	29,30,31,32,33
Serological diagnosis	7	34,35,36,37,38,39,40
Surveillance systems	3	41,42,43
Virological diagnosis	7	15,16,44,45,46,47,48

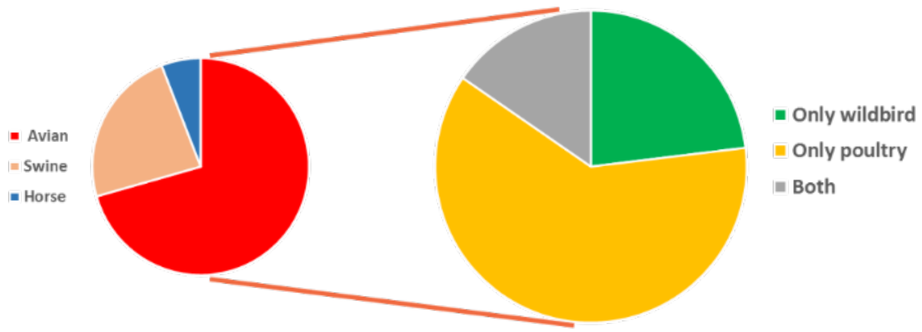

Figure 3. Diagnosis data separated by species and type in case of avian. /*Datos sobre los estudios de diagnóstico estratificados por especies y categorías en el caso de la influenza aviar.*

Social Network Analysis of collaboration

The network of collaboration to generate articles on animal influenza in the Caribbean (Fig. 5) had a size of 23 nodes (countries/ territories) and 129 contacts or edges. Slightly more than 30 % of countries (Cuba, Dominican Republic, Guadeloupe, Haiti, Barbados, France, and Belize) represented 58.89 % of data. Eighty-three of the overall contacts (64.34 %) occurred among Caribbean countries, whereas the remaining 46 edges connected Caribbean countries with European or American nations at a ratio of 32 and 14 respectively. Region interactions were largely represented by France with 55.81 % of relationships, which was six-fold higher than the US as the following most collaborative. Noteworthy, interactions with France were not restricted and were not part of French overseas territories.

The network of collaboration to generate articles on animal influenza at institutional level (Fig. 6) had a size of 51 nodes (institutions) and 350 interactions (edges) distributed mainly into three (3) main communities of nodes with dense connections within each group and sparser connections between different groups. Most of

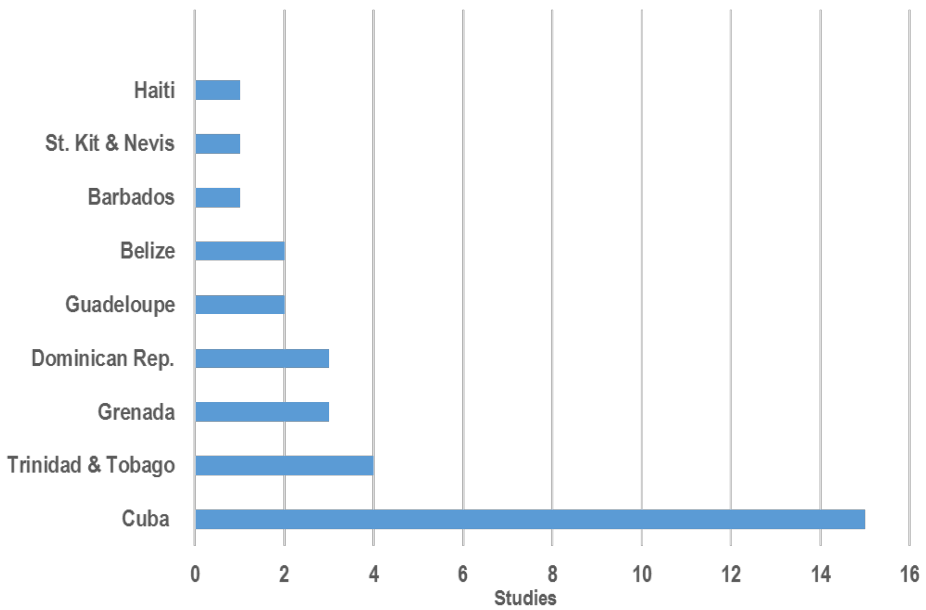

Figure 4. Frequency of studies (articles or disease reports) generated per country within the Caribbean region according to the first author's affiliation. /*Frecuencia de estudios (artículos o notificaciones de enfermedad) generados por país dentro del Caribe, según la afiliación del primer autor.*

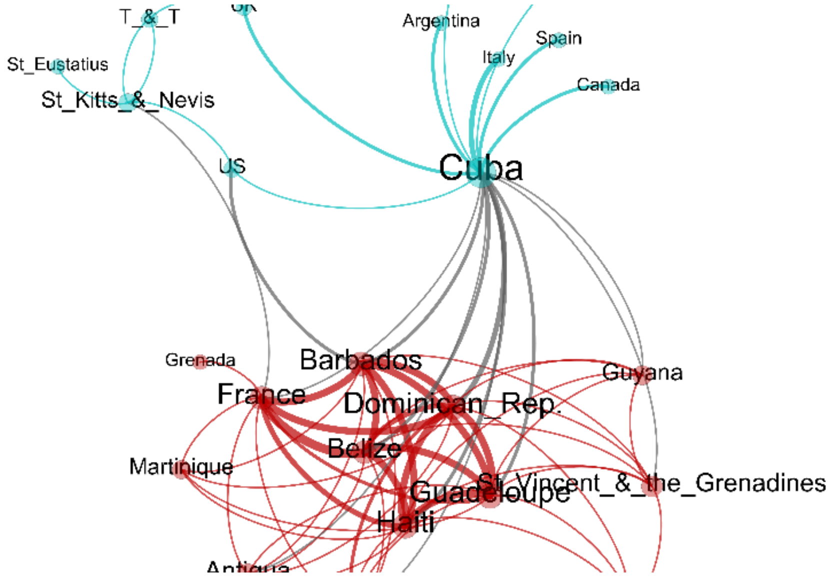

Figure 5. Country/territory contact patterns and intensity of connection within the Caribbean. Size of the nodes and the width of their links are proportional to the degree (number of connections). The nodes and edges with the same color identify a separable community./ *Patrón de contacto e intensidad de conexión entre países y territorios dentro del Caribe. El tamaño de los nodos y el ancho de sus enlaces son proporcionales al grado (número de conexiones). Los nodos y bordes con el mismo color identifican comunidades.*

contacts occurred between Caribbean institutions (61.45 %) followed by other European (24.02 %) and American organizations (14.53 %).

Eight out of 51 (15.69 %) institutions represented over 49 % of the contacts of collaboration, with individual values ranging from 8 % to 4 %. In decreasing order of the degree of contact, these institutions are listed as their acronyms [1], CENSA, MA Barbados,

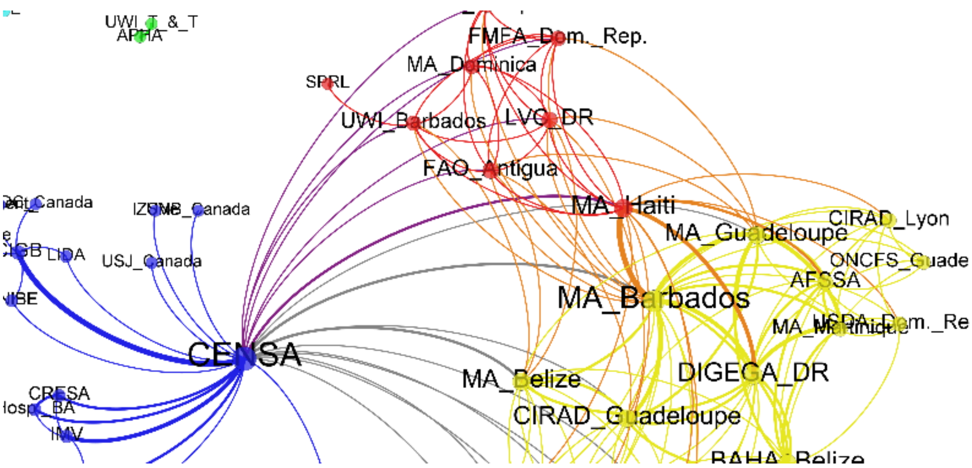

Figure 6. Institutional contact patterns and intensity of connection on animal influenza in the Caribbean. Size of the nodes and the width of their links are proportional to the degree (number of connections). The nodes and edges with the same color identify a separable community./ *Patrones de contacto e intensidad de conexión interinstitucionales sobre influenza animal en el Caribe. El tamaño de los nodos y el ancho de sus enlaces son proporcionales al grado (número de conexiones). Los nodos y bordes con el mismo color identifican una comunidad.*

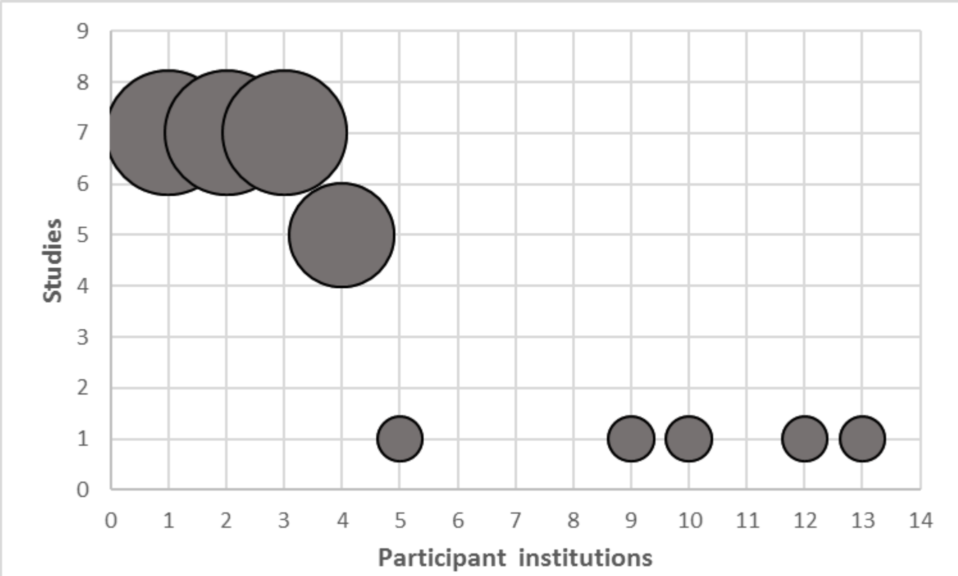

Figure 7. Frequency of studies according to the number of participating institutions. The size of the circles corresponds to the percentage of articles in each class. / *Frecuencia de estudios en función del número de instituciones participantes. El tamaño de los círculos se corresponde con el porcentaje de artículos en cada clase.*

BAHA, DIGEGA DR, MA Haiti, CIRAD Guadeloupe, MA Belize, and MA Guadeloupe.

There was a relative high rate of collaboration in the Caribbean (Fig. 7), which averaged 3.25 participating institution per study. Noteworthy, the 62.50 % of the studies generated more than one institution based on different countries/ territories.

DISCUSSION

The first animal influenza study of wild bird surveillance in Barbados yielded 2 H4N3 AIVs with an isolation rate of 5.0 % (2/40) in hunter-killed Blue-winged teals (45). This study entered the public domain in 2007, but it was carried out between 2003 and 2004, in coincidence with the period of increased awareness of AI. Globally research and surveillance for AIVs increased with the spread of the H5N1 Goose/Guangdong lineage in late 2003s and early 2004s.

However, AI was reported for the first time in the Caribbean in December 2007, when the Dominican Republic determined the presence of an H5N2 LPAIV in poultry (25), as specified by the OIE Terrestrial Animal Health Code (50). Six months later, a similar situation was also confirmed in Haiti (28). In both reports, diagnosis was conducted outside of the affected countries by an OIE Reference Laboratory (National Veterinary Services Laboratories USDA, APHIS, Ames, Iowa, United States).

A subsequent AI event occurred within the Caribbean in 2015, when Belize reported an H5N2 LPAI (24). In this case, confirmation was conducted by an OIE reference laboratory, but affected flocks were first detected under routine serological monitoring implemented as part of a national Avian Influenza Program. This emphasized the importance of having implemented surveillance programs for early alert and appropriate response.

An H5N2 LPAI was reported by the Dominican Republic again in 2017 (26) as well more recently with an unresolved event resulting in seven (7) outbreaks (27). The continuation of Dominican AI reports could be due to the fact that they are reporting on the national infrastructure for diagnosis. Since 2017, the Dominican National laboratory conducted either serology (agar-gel immunodiffusion) or real-time reverse transcriptase/polymerase chain reaction

[1]A complete list of acronyms is provided as supplementary information

(RRT-PCR) in disease outbreak investigations although they continued to submit samples to an OIE reference laboratory.

Interestingly, all AI reports have been caused by the same AIV subtype and pathotype (H5N2 LPAI) (12), since the H5N2 viruses in the Dominican Republic and Haiti, which are closely related to the Mexican lineage of H5N2, which has been circulating in Mexico since early 1994. However, despite of the recurrence of H5N2 LPAI in the Caribbean, detailed phylogenetic analysis of these viruses has not yet been published and virus genetic data are limited to first outbreak in the Dominican Republic (https://www.ncbi.nlm.nih.gov/genbank/). Timely sharing of virological and epidemiological information between the animal and the human health sectors and with other key partners is crucial in developing a better understanding of influenza viruses and their risks, as well as for providing an early warning of emerging threats (51). Six sequences from Dominican outbreaks were submitted to the network of expertise on animal influenza in 2018(52).

The cleavage site within the hemagglutinin precursor protein is the first target of sequencing for both molecular pathotyping and subtyping of AIV(53), (54). However, a larger genome sequencing may also assist to optimize diagnosis through the assessment of mismatches in the primer/probe recognition region as it has occurred (21,55). In addition, it is also important to determine either the genetic evidence of antiviral resistance or molecular markers of interspecies transmission (3,56,57,58), which might have public health implications.

The small number of Caribbean studies on animal influenza in other than avian species could be related to the fact that detections of swine influenza viruses (SIVs) are not officially notifiable to the OIE. Hence, information on its occurrence could go unnoticed when no local arrangements for surveillance are made. While SIV is not officially reportable, it can significantly impact swine production and can have public health implications. It is well acknowledged that swine are often present worldwide at the human-animal interface and maintain a reservoir for antigenically divergent hemagglutinin and neuraminidase proteins that pose a risk for pandemic emergence(52).

Availability of funds could be another reason for few studies on SIV. Noteworthy, all studies reported in the Caribbean (47,46,48) occurred later than the emergence of the swine-origin H1N1 pandemic virus, which could both have attracted attention and mobilize funds to survey SIV. In some studies (46,47), there was financial support provided by a FAO technical cooperation project (TCP/RLA/3206).

Equine influenza is not a listed OIE disease, but it is ostensibly regulated in countries where the breeding and racing of horses are a major industry (10). Equine populations in the Caribbean are not high, as only three (3) countries, namely Cuba, Haiti and the Dominican Republic, have populations between half a million and one million (17).

As it was shown herein, animal influenza studies had an upward trend from 2007 to March 2019. However, publications were concentrated in only a few countries/territories, which constrained their spatial distribution. A decreasing effect on the spatial distribution metric could be present, since studies were consigned according to the first author's country/territory. It is worth noting that 4 studies had regional coverage (15,16,23,43) with another study, on EIV, included 3 Leeward Island (34). Regardless, their importance could be negligible, because they represented a minimal proportion of the reported data (7.14 %).

The high number of articles from Cuba (almost fourfold over the second highest country) could be associated to the thematic diversity and the amount of local institutions working on the subject. At country level, thematic diversification is considered a driver of the productivity or efficiency of the research system (59). Additionally, either the overall or particular differences by topic between and among countries/territories could also be influenced by the success of the scientific technical innovation policy regarding certain topics, expressed in institutions, associated scientific community, presence of the subject in scholarship, and articulation of the science and decision makers (Nuñez, 2019 pers com).

Considering the huge dissimilarities among the Caribbean countries/territories in terms of surface, economies and animal populations (FAOSTAT), it is hard to ascertain the accurate scattering of research and surveillance. However, according to the shape of the retrieved studies, a broader spatial distribution of surveillance efforts on animal influenza is advisable. The scarce surveillance for AIVs in Latin America and the Caribbean is related to the lack of adequate resources and local infrastructure, as well as more urgent animal health priorities (60). Noteworthy, a coordinated surveillance system with a global or a regional perspective does not necessarily require participation from every country (61).

In case of a suspicious disease, reference laboratories support diagnosis, but sustainable surveillance requires local capacities. Alternatively, there are cheap and easy-to-implement serological approaches, such as agar gel precipitation (AGP), that are effective for surveillance, as demonstrated by the detection in Belize (24). Since AIVs exist commonly in wild free flying ducks as LPAI viruses (5,6), subclinical infections in poultry are more difficult to detect. Consequently, LPAI surveillance often relies on diagnostic tests, particularly serology, and molecular and virological tests are used to follow up positive cases (51).

A better understanding of AIV research and surveillance will aid in risk assessment. Progress has been made in surveillance reporting in this region (42); however, ongoing work for avian influenza needs to be strengthened (https://www.caribvet.net/).

The interaction between animals and humans is a major source of emerging infectious diseases, some of which have the potential to cause global pandemics in the future (62). From the One Health perspective, one of the major concerns for IAVs are intermediate hosts that have dual specificity sialic acid receptors on their cells (e.g. swine and domestic poultry (quails and turkeys)), which may be involved in the interspecies transfer of influenza viruses (3). Under circumstances of interaction among such species with humans, there are also opportunities for reassortment of the genes from these viruses, which may result in a mammalian-adapted influenza virus. In contrast, influenza surveillance in production animals is largely focused on facilitating the international trade (14).

Some global spatial frameworks have been developed to quantify the geographic variation in outbreak emergence based on potential species transmission to humans (11,63), but they have been scarcely implemented at regional or national level with lower spatial resolution.

Network analysis from a social science perspective was developed to characterize a group of authors and the nature and extent of the connections or interactions between and among them. In the current work, the SNA program allowed to identify the most productive countries/territories and institutions, as well as the identification of groups of them with more intense collaboration, which have published studies on animal influenza through the period 2007-March 2019. It was confirmed the 'same country or institution phenomenon', which might be because scientists and researchers in the same country or institution have the quickest and easiest ways to communicate, and further form collaborative relationship (64). However, it was remarkable that 62.50 % of the studies were generated from institutions based on more than one country/territory. Research collaborations contribute to the advancement of knowledge by exploiting the results of scientific efforts more cost-effectively and also enhance the sharing of resources among nations and disciplines (65).

CONCLUSIONS

Reported studies of animal influenza in the Caribbean have tended to increase since 2007, but they have been concentrated in a few countries/territories. Such constrained spatial distribution may constitute gaps in the early alert capacity of the existence of these viruses, which in turn may threaten both human and animal health for optimizing pandemic mitigation strategies. A better balance of surveillance efforts in the short term may increase country/territory capacities to implement feasible and low-cost approaches to constrain or eliminate the threat. The spatial risk assessment of animal influenza and further design of risk-based sampling can optimize resources for animal influenza surveillance in this region. This systematic review suggested the need to further expand the scientific studies on animal influenza generated in the Caribbean and the opportunities to improve risk assessment, management and communication through international collaboration.

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REFERENCES

1. Short KR, Richard M, Verhagen JH, van Riel D, Schrauwen EJA, van den Brand JMA, *et al*. One health, multiple challenges: The inter-species transmission of influenza A virus. One Health. 2015;1:1-13.
2. Morens DM., Taubenberger JK. Historical thoughts on influenza viral ecosystems, or behold a pale horse, dead dogs, failing fowl, and sick swine. Influenza Other Respir Viruses. 2010;4(6):327-337.
3. Webster RG, Govorkova EA. Continuing challenges in influenza. Ann N Acad Sci. 2014;1323(1):115-139.
4. WHO. Avian and other zoonotic influenza. [Internet]. 2019. Disponible en: https://www.who.int/influenza/human_animal_interface/en/
5. Swayne DE. Understanding the Complex Pathobiology of High Pathogenicity Avian Influenza Viruses in Birds. Avian Dis. 2007;51(s1):242-249.
6. Alexander DJ. Summary of avian influenza activity in Europe, Asia, Africa, and Australasia, 2002-2006. Avian Dis . 2007;51(s1):161-166.
7. Xie T, Anderson BD, Daramragchaa U, Chuluunbaatar M, Gray GC. A Review of Evidence that Equine Influenza Viruses Are Zoonotic. Pathogens [Internet]. 2016;5(50). Disponible en: http://www.mdpi.com/journal/pathogens
8. Crawford PC, Dubovi EJ, Castleman WL, Stephenson I, Gibbs EPJ, Chen L, *et al*. Transmission of equine influenza virus to dogs. Science. 2005;310:482-485.
9. Parrish CR, Murcia PR, Holmes EC. Influenza Virus Reservoirs and Intermediate Hosts: Dogs, Horses, and New Possibilities for Influenza Virus Exposure of Humans. J Virol. 2015;89(6):2990-2994.
10. Gibbs EPJ, Anderson TC. Equine and canine influenza: a review of current events. Anim Health Res Rev. 2010;11(1):43-51.
11. Berger KA, Pigott DM, Tomlinson F, Godding D., Maurer-Stroh S, TayeB, *et al*. The geographic variation of surveillance and zoonotic spillover potential of influenza viruses in domestic poultry and swine. Open Forum Infect Dis. 2018;5(12),ofy318:1-9.ofy318. doi: 10.1093/ofid/ofy318
12. Senne DA. Avian Influenza in North and South America, the Caribbean, and Australia, 2006-2008. AVIAN Dis. 2010;54:79-186.
13. Acevedo AM, Santana E, Díaz de Arce H, Pérez LJ, Caballero A, Suárez L, *et al*. Development of positive controls for molecular methods of avian influenza virus detection. Rev Salud Anim. 2009;31(1):50-54.
14. von Dobschuetz S, De Nardi M, Harris KA, Munoz O, Breed AC, Wieland B, *et al*. Influenza surveillance in animals: what is our capacity to detect emerging influenza viruses with zoonotic potential? Epidemiol Infect. 2015;143(10):2187-2204.
15. Lefrançois T, Hendrikx P, Ehrhardt N, Millien M, Gomez L, Gouyet L, *et al*. Surveillance of Avian Influenza in the Caribbean Through the Caribbean Animal Health Network: Surveillance Tools and Epidemiologie Studies. Avian Dis . 2010;54(1):369-373.
16. Lefrançois T, Hendrikx P, Vachiery N, Ehrhardt N, Millien M, Gomez L, *et al*.Interaction between research and diagnosis and surveillance of avian influenza within the Caribbean animal health network (CaribVET). TransboundEmerg Dis. 2010;57:11-14.
17. FAOSTAT. FAOSTAT Food and agriculture data [Internet]. 2019. Disponibleen: http://www.fao.org/faostat/es/#data/QL

18. Kelman I, Lewis J. Ecology and vulnerability: islands and sustainable risk management. Int J IslAff. 2005;14(2):4-12.
19. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, *et al*. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Med. 2009;6(7):e1000100.
20. Acevedo AM, Lazo AM, Relova D, Perera CL, Acevedo AM, Lazo AM, *et al*. Standarization of a SYBR Green-I based real time RT-PCR assay for the detection of equine influenza virus. Rev Salud Anim . 2018; 40(3):1-7.
21. Perez LJ, Diaz de Arce H, Cilloni F, Salviato A, Marciano S, Perera CL, *et al*.An SYBR Green-based real-time RT-PCR assay for the detection of H5 hemagglutinin subtype avian influenza virus. Mol CellProbes. 2012;26:137-145.
22. Relova D, Rios L, Acevedo AM, Coronado L, Perera CL, Pérez LJ. Impact of RNA Degradation on Viral Diagnosis: An Understated but Essential Step for the Successful Establishment of a Diagnosis Network. Vet Sci. 2018;5(19).
23. Percedo MI, Guitian J, Herbert-Hackshaw K, Pradel J, Bournez L, Petit-Sinturel M, *et al*. Developing a disease prevention strategy in the Caribbean: the importance of assessing animal health-related risks at regional level. Rev Sci Tech-Off Int Epizoot. 2011;30(3):725-731.
24. DePaz MA. Low pathogenic avian influenza (poultry), Belize [Internet]. WAHIS; 2015. Disponible en: https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=17037
25. Quiñónes RA. Low pathogenic avian influenza (poultry), Dominican Republic [Internet]. WAHIS; 2007. Disponible en: https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=6616
26. Gómez NL. Low pathogenic avian influenza (poultry), Dominican Republic [Internet]. WAHIS; 2017. Disponible en: https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=25099
27. Gómez NL. Low pathogenic avian influenza (poultry), Dominican Republic [Internet]. WAHIS; 2019. Disponible en: https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=29149
28. Millien M. Report Immediate notification OIE: Low pathogenic avian influenza (poultry). [Internet] Haiti: WAHIS. 2008. Disponible en: http://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=7116
29. Ceballo Y, Tiel K, Lopez A, Cabrera G, Perez M, Ramos O, *et al*.High accumulation in tobacco seeds of hemagglutinin antigen from avian (H5N1) influenza. Transgenic Res. 2017;26:775-789.
30. Pose AG, Gomez JN, Sanchez AV, Redondo AV, Rodriguez ER, Segui RM, *et al*.Subunit influenza vaccine candidate based on CD154 fused to HAH5 increases the antibody titers and cellular immune response in chickens. Vet Microbiol. 2011;152:328-337.
31. Pose AG, Morell NO, Matos DA, Rodriguez ER, Rodriguez ES, Cordero LR, *et al*. Stable lentiviral transformation of CHO cells for the expression of the hemagglutinin H5 of avian influenza virus in suspension culture. Biotechnol Rep Amst. 2014;3:108-116.
32. Pose AG, Rodriguez ES, Mendez AC, Gomez JN, Redondo AV, Rodriguez ER, *et al*. Dual function of the hemagglutinin H5 fused to chicken CD154 in a potential strategy of DIVA against avian influenza disease: preliminary study. Open Vet J. 2015;5:138-147.
33. Pose AG, Rodriguez ER, Pineiro MJ, Montesino R, Sanchez O, Toledo JR. Quantitative ELISA sandwich for a new vaccine against avian influenza virus H5N1. J Immunol Methods. 2018;459:70-75.
34. Bolfa P, Jeon I, Loftis A, Leslie T, Marchi S, Sithole F, *et al*. Detection of West Nile Virus

and other common equine viruses in three locations from the Leeward Islands, West Indies. Acta Trop. 2017;174:24-28.

35. Brown A, Bolfa P, Marchi S, Hemmings S, Major T, Suepaul R, *et al*. Detection of Antibodies to Seven Priority Pathogens in Backyard Poultry in Trinidad, West Indies. Vet Sci . 2018;5(1):11.

36. Brown A, Sookhoo J, Blake L, Crooks P, Mohammed Z, Molawatti-Bisnath J, *et al*. Serological evidence for eight globally important poultry viruses in Trinidad & Tobago. Prev Vet Med. 2018;149:75-81.

37. Brown A, Narang D, Essen SC, Brookes SM, Brown IH, Oura C. Serological Evidence for Influenza A Virus Exposure in Wild Birds in Trinidad & Tobago. Vet Sci . 2018;5:50.

38. Sharma RN, Tiwari KP, Chikweto A, Thomas D, DeAllie C, Stratton G, *et al*. Seroprevalence of five important viral diseases in commercial chickens in Grenada, West Indies. Int J Poult Sci. 2014;13(5):299-303.

39. Sharma RN, Bréjeon A, Bruyant S, Tiwari K, Chikweto A, Bhaiyat MI. Seroprevalence of Newcastle Disease, Chicken Infectious Anemia and Avian Influenza in Indigenous Chickens in Grenada, West Indies. J Anim Res V. 2015;5(1):1-5.

40. Sookhoo JRV, Brown-Jordan A, Blake L, Holder RB, Brookes SM, Essen S, *et al*. Seroprevalence of economically important viral pathogens in swine populations of Trinidad and Tobago, West Indies. Trop Anim Health Prod. 2017;49:1117-1124.

41. Ferrer E, Calistri P, Fonseca O, Ippoliti C, Alfonso P, Iannetti S, *et al*.Estimation of the sensitivity of the surveillance system for avian influenza in the western region of Cuba. Vet Ital. 2013;49(1):99-107.

42. Ferrer E, Alfonso P, Ippoliti C, Abeledo M, Calistri P, Blanco P, *et al*. Development of an active risk-based surveillance strategy for avian influenza in Cuba. Prev Vet Med . 2014;116:161-167.

43. Gongora V, Trotman M, Thomas R, Max M, Zamora PA, Lepoureau MT, *et al*. The Caribbean animal health network: new tools for harmonization and reinforcement of animal disease surveillance. Ann N Y Acad Sci. 2008;1149:12-15.

44. Sabarinath A, Sabarinath GP, Tiwari KP, Kumthekar SM, Thomas D, Sharma RN, *et al*. Virological and serological surveillance of avian influenza virus in the birds of Grenada. Int J Poult Sci . 2011;10(8):579-582.

45. Douglas KO, Lavoie MC, Mia Kim L, Afonso CL, Suarez DL. Isolation and genetic characterization of avian influenza viruses and a Newcastle disease virus from wild birds in Barbados: 2003-2004. Avian Dis . 2007;51(3):781-787.

46. Pérez LJ, Perera CL, Vega A, Frías MT, Rouseaux D, Ganges L, *et al*. Isolation and complete genomic characterization of pandemic H1N1/2009 influenza viruses from Cuban swine herds. Res VetSci. 2013;94(3):781-788.

47. Pérez LJ, Perera CL, Coronado L, Riosa L, Vega A, Frías MT, *et al*. Molecular epidemiology study of swine influenza virusrevealing a reassorted virus H1N1 in swine farms in Cuba. PrevVetMed. 2015;119(3-4):172-178.

48. Vega A, Perera CL, Díaz de Arce H, Frías MT, Pérez LJ. Aislamiento de virus influenza porcina en Cuba. Rev Salud Anim . 2012;34(2):127-130.

49. Brown JD, Swayne DE, Cooper RJ, Burns RE, Stallknecht DE. Persistence of H5 and H7 avian influenza viruses in water. Avian Dis . 2007;51(s1):285-289.

50. OIE. Chapter 10.4. Infection with avian influenza viruses. En: In terrestrial animal health code. 2018. Disponible en: http://www.oie.int/fileadmin/Home/eng/Health_standards/tahc/current/chapitre_avian_influenza_viruses.pdf

51. OFFLU. Strategy document for surveillance and monitoring of influenzas in animals. 2013. Disponible en: http://www.offlu.net/fileadmin/home/en/publications/pdf/OFFLUsurveillance.pdf

52. OFFLU. Annual Report 2018. 2018. Disponible en: http://www.offlu.net/fileadmin/home/en/publications/pdf/OFFLU_Annual_Report_2018.pdf

53. Gall A, Hoffmann B, Harder T, Grund C, Beer M. Universal Primer Set for Amplification and Sequencing of HA0 Cleavage Sites of All Influenza A Viruse. J ClinMicrobiol. 2008;46(8):2561-567.

54. Leijon M, Ullman K, Thyselius S, Zohari S, Pedersen JC, Hanna A, *et al*. Rapid PCR-Based Molecular Pathotyping of H5 and H7 Avian Influenza Viruses. J ClinMicrobiol . 2011;49(11):3860-3873.
55. Suarez DL. Evaluation of primer and probe mismatches in sensitivity of select RRT-PCR tests for avian influenza [abstract]. Am Assoc Avian Pathol Meet July 16-19 2011 St Louis Mo CD-ROM. 2011. Disponible en: https://www.ars.usda.gov/research/publications/publication/?seqNo115=269060
56. Govorkova EA, Baranovich T, Seiler P, Armstrong J, Burnham A, Guan Y, *et al*. Antiviral resistance among highly pathogenic influenza A (H5N1) viruses isolated worldwide in 2002-2012 shows need for continued monitoring. Antiviral Res. 2013;98(2):297-304.
57. Lloren KKS, Lee T, Kwon JJ, Song M-S. Molecular Markers for Interspecies Transmission of Avian Influenza Viruses in Mammalian Hosts. Int J Mol Sci. 2017;18(12):2706.
58. Zanin M, Wong S-S, Barman S, Kaewborisuth C, Vogel P, Rubrum A, *et al*. Molecular basis of mammalian transmissibility of avian H1N1 influenza viruses and their pandemic potential. Proc Natl Acad Sci U S A. 2017;114(42):11217-11222.
59. Cimini G, Gabrielli A, Sylos F. The Scientific Competitiveness of Nations. PLoS ONE. 2014;9(12)(e113470).
60. Gonzalez-Reiche AS., Perez DR. Where Do Avian Influenza Viruses Meet in the Americas? AvianDis. 2012;56:1025-1033.
61. Machalaba CC, Elwood SE, Forcella S, Smith KM, Hamilton K, Jebara KB, *et al*. Global Avian Influenza Surveillance in Wild Birds: A Strategy to Capture Viral Diversity. Emerg Infect Dis. 2015;21(4). http://dx.doi.org/10.3201/eid2104.141415
62. Morse SS, Mazet JA, Woolhouse M, Parrish CR, Carroll D, Karesh WB, *et al*. Zoonoses 3: Prediction and prevention of the next pandemic zoonosis. The Lancet. 2012;380(9857):1956-965.
63. Hill AA, Dewé T, Kosmider R, von Dobschuetz S, Munoz O, Hanna A, *et al*. Modelling the species jump: towards assessing the risk of human infection from novel avian influenzas. R Soc Open Sci. 2015;2(9). http://rsos.royalsocietypublishing.org/
64. Li C, Hatta M, Burke DF, Ping J, Zhang Y, Ozawa M, *et al*. Selection of antigenically advanced variants of seasonal influenza viruses. Nat Microbiol. 2016;1(6):16058.
65. Zhang C, Yu Q, Fan Q, Duan Z. Research collaboration in health management research communities. BMC Med Inform Decis Mak. 2013;13(1):52.

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