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Evaluation of Avian Papillomavirus Occurrences and Effective Sampling Materials for Screening Purpose in Bird Species Through Systematic Review and Meta-Analysis

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ABSTRACT

Papillomaviruses (PVs), double-stranded circular DNA viruses, typically cause regressing papillomas (warts) on mucosal or keratinized epithelia of a wide spectrum of species. The viruses largely infect mammals, whereby PV infections in humans, bovines, and rabbits are extensively reported. However, studies on non-mammalian PVs, particularly avian ones, are relatively lacking and worthy of investigation. This study performed a meta-analysis post-systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines to evaluate the occurrences of avian papillomaviruses (APVs) in bird species and effective materials used for virus detection. The electronic databases Science

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Direct, Medline via PubMed, and Google Scholar were used to search for the journal articles. Upon article eligibility check, the QUADAS-2 was employed to assess the data. Of 1139 records, 31 were eligible for full-text review, but only 9 were significant for the final review. The results showed that APVs are highly prevalent among the Fringillidae family, with a proportion of 81%, followed by Laridae (30%) and Anatidae (13%). The pooled prevalence of APV in tissue samples was 38%, while in swab samples was 13%. Only one study reported positive APV from fecal materials (0.4%); hence, the reliability comparison between these three samples was not performed. This study concluded that APVs are most prevalent in the Fringillidae bird family, while tissues are the most suitable biological samples for APV screening and should be considered as a single sample material. From epidemiology, knowledge of APV incidences and distribution may assist in controlling papillomatosis in bird species.

Keywords: Avian, bird, meta-analysis, papillomavirus, virus

INTRODUCTION

Papillomaviruses (PVs) are relatively small, non-enveloped, icosahedral viruses belonging to the family *Papillomaviridae*. PVs contain circular double-stranded DNA with a complete genome size ranging from 6.9 to 8.6 kb. The genome is divided into three codon regions (early, E; late, L; and long codon region, LCR) that encode the replication proteins E1, E2, E4, the oncoproteins E5, E6, and E7, and the capsid proteins L1 and L2 (Araldi et al., 2017). More than 130 species in more than 50 genera of PV were identified (Canuti et al., 2019). Most PVs are detected in mammals; however, the number of PVs detected in birds is increasing. To date, 11 complete genomes and 9 partial sequences of avian papillomaviruses (APVs) have been reported. The APV with complete genome sequences were discovered in chaffinch (FcPV1) (Terai et al., 2002), Northern fulmar (FgPV1) (Gaynor et al., 2015), yellow-necked francolin (FlPV1) (Van Doorslaer et al., 2009), Adélie penguin (PaPV1 and PaPV2) (Varsani et al., 2014), African gray parrot (PePV1) (Tachezy et al., 2002), and Yorkshire canary (ScPV1) (Truchado, Moens, et al., 2018). The complete genome sequence of APV was identified in Atlantic puffin (PuPV-1), American herring gull (GuPV-1), mallard and American black duck (DuPV-3), and black-legged kittiwake (KiPV-2), while APV with partial sequence were identified in mallard (Duck PV), gull (GuPV-2 and GuPV-3), and black-legged kittiwake (KiPV-1, KiPV-3, KiPV-4, KiPV-5, KiPV-6, and KiPV-7) (Canuti et al., 2019).

PVs primarily infect and replicate in the mucosal and keratinized epithelia, which may induce the development of benign and malignant neoplastic lesions. The lesions or neoplasms are discovered in various body parts among different bird species. Chaffinch papillomatosis is cauliflower-shaped neoplasms on the tarsi and digits (Lina et al., 1973). Small featherless wartlike growths were found in the unfeathered areas around the canary's beak (Dom et al., 1993). Cutaneous papilloma-like lesions

in African gray parrots are discovered on the beak's head, eyelids, and commissure (Latimer et al., 1997). However, APV was also discovered in the healthy skin of a yellow-throated francolin (Van Doorslaer et al., 2009) and non-obvious lesions in the oral mucosa and tongue of a captive Yorkshire canary (Truchado, Moens, et al., 2018). Papilloma-like lesions also appeared in the legs of some bird species with no APV detected (Katoh et al., 2010).

Knowledge regarding APV prevalence is still very limited; thus, efforts need to be made to increase the sampling and screening of APV. Several diagnosis methods were implemented to identify APV. The first identification of APV was demonstrated using electron microscopy in the 1970s (Lina et al., 1973). The virus was examined in the nuclei of cells isolated from proliferative lesions on the legs of chaffinches (*Fringilla coelebs*). Electron microscopy also revealed leg papillomatosis in six chaffinches in the Czech Republic and one in Germany (Literák et al., 2003). Molecular technique such as PCR is developed to detect the presence of the virus in griffon vultures (Di Francesco et al., 2019), ducks (Williams et al., 2018), and other wild birds (Canuti et al., 2019; Padzil et al., 2022). The viruses were detected from various sample types, including skin, internal epithelium, fecal material, and oropharyngeal and cloacal swabs (Truchado, Williams, et al., 2018). PVs are highly host-specific DNA viruses; thus, the immunity is species-specific (King et al., 2011). Although data on APV prevalence are still very limited, a significant number of non-human PVs were identified in different species, especially birds. A proper diagnosis method and appropriate sample materials are needed to detect APV. Therefore, the objectives of this meta-analysis are to observe the distribution of APV in bird species and to determine the prevalence of APV in different sample materials. Thus, the most favorable biological sample type for APV screening can be determined.

MATERIALS AND METHODS

Protocol and Search Strategy

The protocol for the systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines to specify the search strategy, eligibility criteria, objectives, and methods (Moher et al., 2009). The electronic databases Science Direct, Medline via PubMed, and gray literature (Google Scholar) were searched for papers published in any year. The following terms were used: "papillomavirus", "avian papillomavirus", "avian papillomavirus prevalence", or "avian papillomavirus detection". Reference lists cited in all article searches were also checked. An updated search was performed on November 13, 2020. Relevant citations from each database were extracted, and duplicate files were removed.

Eligibility Criteria

Titles and abstracts retrieved from journal articles were screened for eligibility. All the relevant journal articles were reviewed in full text, and those fulfilling inclusion criteria

were extracted for their data. All abstracts were screened by one author (NN). The journal articles were included if they met all the following eligibility criteria: (1) targeted PV in all avian species at any ages, not in human or other non-mammalian species, (2) screened using any laboratory-confirmed methods, (3) used any sample materials, and (4) published in English in any year. Studies that did not clearly state the presence of PVs in the avian species were excluded.

Data Extraction and Bias Assessment

Data extracted from the included studies were compiled in a developed data extraction sheet. Table 1 shows the information extracted from the selected studies. The risk of bias in each study was assessed using the Diagnostic Precision Study Quality Assessment Tool (QUADAS-2) recommended by the Cochrane Collaboration.

Data Analysis

The random effects model meta-analysis method was used to analyze the pooled prevalence of APV in different avian species and sample materials. The heterogeneity among the studies was analyzed using the Higgins test (I^2), which shows the percentage of variation among studies (Higgins et al., 2003). These analyses were compiled using the Review Manager Software (version 5.4) (Moher et al., 2009). The odds ratio (OR) test, with a 95% confidence interval (95% CI), was calculated to measure the probability of APV infection for symptomatic compared to asymptomatic birds.

RESULTS

Search results returned a total of 1,170 articles after duplicate removal. Of these, 1,139 studies were excluded due to irrelevant titles and abstracts during screening, while 31 were eligible for full-text review. After full-text articles were extracted, only nine studies indicated the presence of PVs in the avian species. Therefore, only these studies were considered completely relevant and thus included in the final review (Canuti et

Table 1
Datasheet extracted from articles and records included in this systematic review

Data	Range
Year	Any year
Sample taken	Avian species only
Sample size	1–500
Symptoms	General symptoms Appearance of papilloma Appearance of lesion Respiratory problem Dead Other Asymptomatic
Stages of samples	Juvenile Adult Other
Epidemiological unit	Wild bird species Wild habitat Zoo Natural park
Method of testing	Histopathology Molecular Combination (Histopathology and molecular)
Sample type	Biopsy Swab Feces Mixed
Avian papillomavirus prevalence	0–100%

al., 2019; Dom et al., 1993; Latimer et al., 1997; Pérez-Tris et al., 2011; Prosperi et al., 2016; Sironi & Gallazzi, 1992; Truchado, Williams, et al., 2018; Van Doorslaer et al., 2017; Williams et al., 2018). The result of the search strategy is shown in a PRISMA flow chart (Figure 1).

The included studies were published from 1992 to 2019. Despite the 27 years of time scale, the limited relevant studies affirm the insufficient knowledge of PVs in avian species. Out of nine, two studies were conducted in the United States and Italy, whereas Spain, Georgia, Sweden, Canada, and Belgium contributed with one study each. Six studies mentioned that symptoms appeared on the collected birds, while three did not report whether the birds were symptomatic or asymptomatic. The information on the stages and sex of the birds was insufficiently provided in all studies, so the criteria were not reported here. Meta-analysis of diagnostic accuracy of the APV detection methods was also not performed in this study due to inadequate data, such as sensitivity value, specificity value, true/false-positive value, and true/false-negative value.

Nine studies screened for APV from 711 bird samples of 47 different specified species and 3 unspecified species. The APV was detected in 17 species that are categorized under 6 families. Among the family Alcidae, *Fratercula arctica* was detected with a prevalence of 9.8%. Two studies detected APV in the family Anatidae, with four species (American black duck × mallard hybrid, *Anas platyrhynchos*, *Anas platyrhynchos domesticus*, and *Anas rubripes*) that were positive for APV infection. Four species among the family Fringillidae that showed positive APV

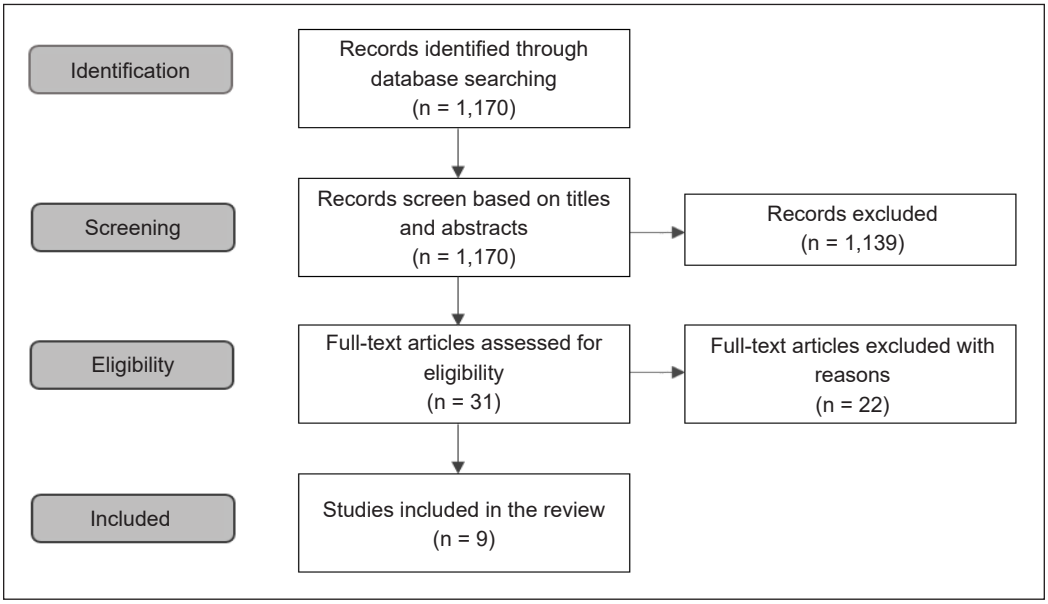


Figure 1. The process of article selection is based on PRISMA. Out of 31 eligible articles, only 9 reported on APV infection and thus were included in the final review

infection were *Carduelis chloris*, *Fringilla coelebs*, *Fringilla montifringilla*, and *Serinus canaria*, whereas the viruses were detected in three species among the family Laridae, namely, *Larus marinus*, *Larus smithsonianus*, and *Rissa tridactyla*. The families of Psittacidae, Spheniscidae, and Sylviidae had one species detected with PV infections: *Psittacus erithacus*, *Pygoscelis adeliae*, and *Sylvia atricapilla*. Table 2 presents the distribution of APV in the collected birds according to their species.

Among the included studies, five performed APV screening on the wild birds, whereas four performed screening at the aviary, with one performed screening on both wild and captive birds. One study performed the screening using archived tissue samples. The pooled prevalence of APV can be analyzed among the families Anatidae (duck species), i.e., 13% (95% CI = −0.03–0.29, I^2 = 90%), Fringillidae, i.e., 81% (95% CI = 0.56–1.05, I^2 = 0%), and Laridae, i.e., 30% (95% CI = 0.04–0.56, I^2 = 96%) (Figure 2).

Five studies included the descriptions of APV in biopsy samples from symptomatic birds. Seven types of biopsy samples involved a total of 43 samples, which were skin (n = 10), larynx/trachea (n = 2),

Table 2
Distribution of avian papillomavirus in the collected birds according to their species. Out of 798 birds of various species reported by nine studies, 95 were positive for APV

Family	Bird species	Number of bird sample	Number of birds with positive APV	Reference
Alcidae	*Alca torda*	30	0	Canuti et al. (2019)
	Fratercula arctica	51	5	
	Uria aalge	41	0	
	Uria lomvia	2	0	
Anatidae	American black duck × mallard hybrid	4	1	Canuti et al. (2019)
	Anas crecca	35	0	Williams et al. (2018)
	Anas penelope	1	0	Williams et al. (2018)
	Anas platyrhynchos	246	6	Williams et al. (2018)
		10	1	Canuti et al. (2019)
	Anas platyrhynchos domesticus	17	2	Williams et al. (2018)
	Anas rubripes	102	30	Canuti et al. (2019)
Burhinidae	*Burhinus oedicnemus*	1	0	Pérez-Tris et al. (2011)
Cacatuidae	*Cacatua moluccensis*	2	0	Latimer et al. (1997)
Columbidae	*Ducula oceanica*	1	0	Pérez-Tris et al. (2011)
	Leptotila rufaxilla	1	0	
	Streptopelia orientalis	1	0	
	Cyanocorax yncas	1	0	Pérez-Tris et al. (2011)
Emberizidae	*Emberiza leucocephalos*	1	0	Pérez-Tris et al. (2011)

Table 2 *(continue)*

Family	Bird species	Number of bird sample	Number of birds with positive APV	Reference
Fringillidae	*Carduelis chloris*	1	0	Pérez-Tris et al. (2011)
		2	2	Sironi and Gallazi (1992)
	Euphonia musica	1	0	Pérez-Tris et al. (2011)
	Fringilla coelebs	6	5	Pérez-Tris et al. (2011)
		5	5	Prosperi et al. (2016)
	Fringilla montifringilla	1	1	Prosperi et al. (2016)
	Loxia curvirostra	1	0	Pérez-Tris et al. (2011)
	Pyrrhula pyrrhula	1	0	Pérez-Tris et al. (2011)
	Pyrrhula pyrrhula griseiventris	1	0	Pérez-Tris et al. (2011)
	Serinus canaria	4	3	Truchado, Williams, et al. (2018)
		2	2	Dom et al. (1993)
Laridae	*Larus delawarensis*	9	0	Canuti et al. (2019)
	Larus glaucoides	4	0	
	Larus marinus	38	1	
	Larus smithsonianus	94	16	
	Rissa tridactyla	16	13	
Paridae	*Cyanistes caeruleus*	1	0	Pérez-Tris et al. (2011)
	Parus afer	1	0	Pérez-Tris et al. (2011)
	Periparus ater	1	0	Pérez-Tris et al. (2011)
Passeridae	*Passer domesticus*	7	0	Pérez-Tris et al. (2011)
	Passer griseus	1	0	Pérez-Tris et al. (2011)
Psittacidae	*Amazona aestiva*	1	0	Latimer et al. (1997)
	Amazona amazonica	1	0	Latimer et al. (1997)
	Amazona autumnalis	1	0	Latimer et al. (1997)
	Amazona farinosa	1	0	Latimer et al. (1997)
	Amazona ochrocephala	1	0	Pérez-Tris et al. (2011)
		1	0	Latimer et al. (1997)
	Amazona ochrocephala auropalliata	2	0	Latimer et al. (1997)
	Amazona sp. - unspecified	4	0	Latimer et al. (1997)
	Ara ararauna	6	0	Latimer et al. (1997)
	Ara chloroptera	1	0	Latimer et al. (1997)
	Ara sp. - unspecified	2	0	Latimer et al. (1997)
	Aratinga erythrogenys	1	0	Latimer et al. (1997)
	Aratinga sp. - unspecified	2	0	Latimer et al. (1997)
	Psittacus erithacus	2	1	Latimer et al. (1997)
Spheniscidae	*Pygoscelis adeliae*	25	1	Van Doorslaer et al. (2017)
Sylviidae	*Sylvia atricapilla*	3	0	Pérez-Tris et al. (2011)

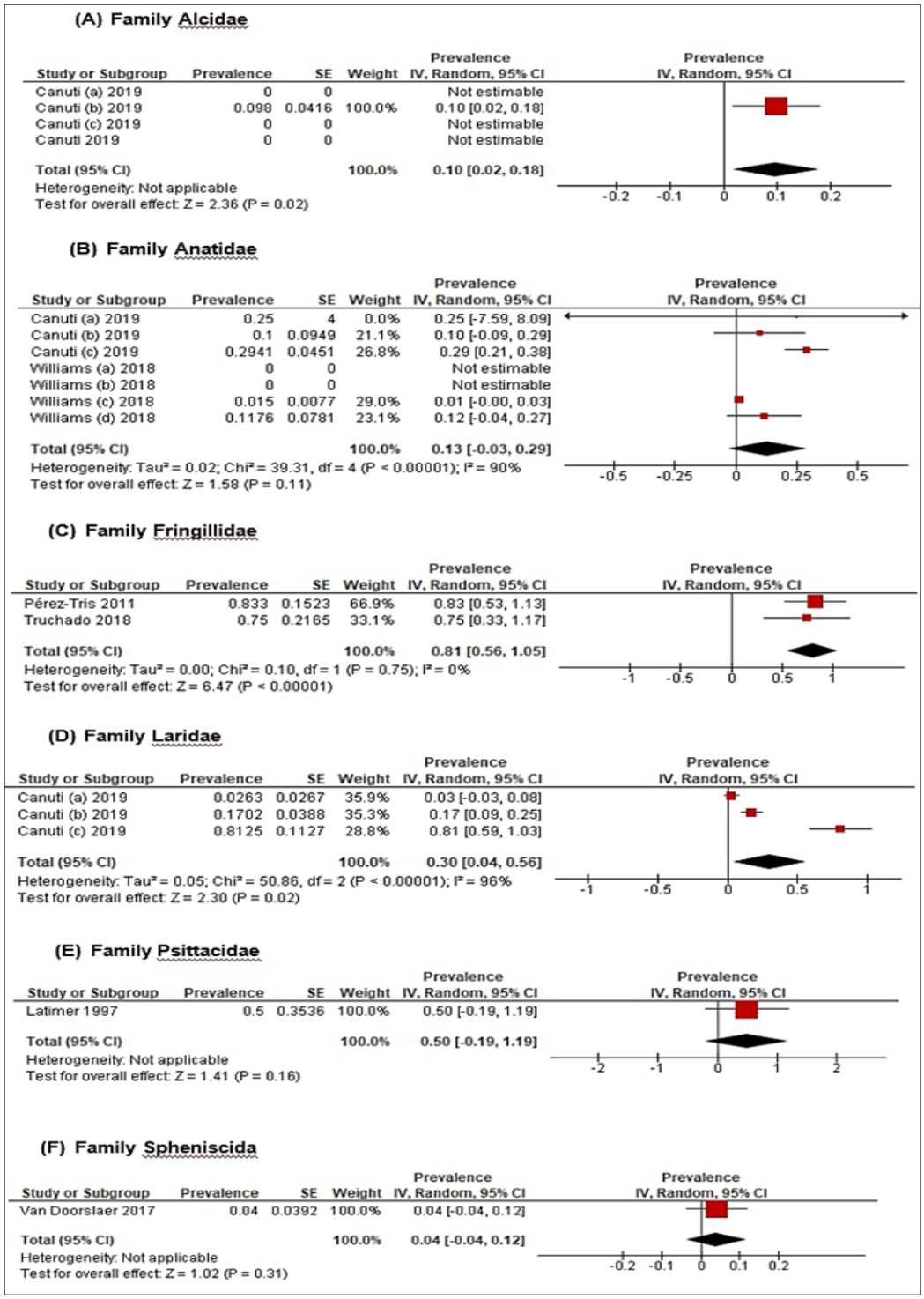


Figure 2. Forest plot of random-effect meta-analysis of avian papillomavirus in different bird families. Data shows that APVs are highly prevalent among the Fringillidae family, followed by Laridae and Anatidae

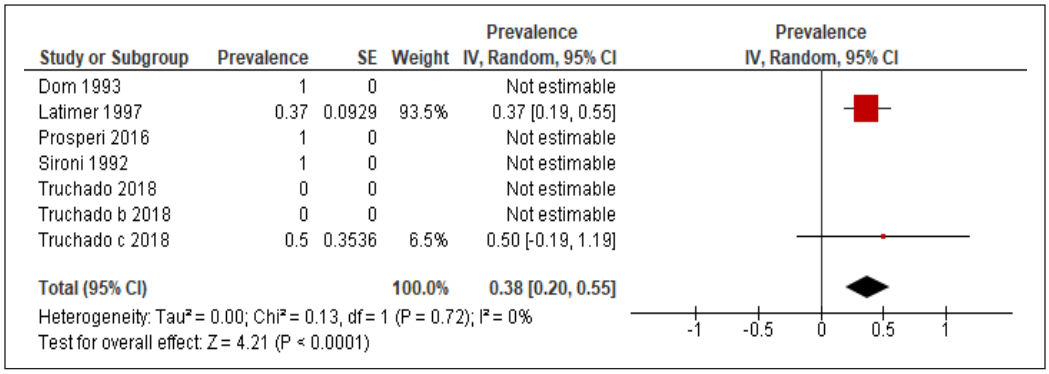
digestive tract (n = 2), tongue (n = 2), and cloacal/oral (n = 27). Of these, 12 samples were positive for APV infection, with 10 from the skin, 1 from the tongue, and 1 from cloacal/oral papilloma. Skin biopsies were performed in three studies, whereas other types of biopsy samples were reported by one individual study separately. Only one study screened APV in three biopsy samples: larynx/trachea, digestive tract, and tongue. The high prevalence of APV on bird skins corresponds to the known type of human cutaneous PV, represented by the beta and gamma genera, which reside widely on the skin surface. Therefore, a similar skin commensalism/mutualism between APV with their avian hosts and APV occurrences would best be diagnosed by symptom manifestations on the skin is proposed.

Four studies included descriptions of APV in swab samples. Three types of swab samples involved a total of 641 samples, which were oral swabs (n = 164), cloacal swabs (n = 25), and paired oropharyngeal and cloacal swabs (n = 452). Of these, 96 samples were positive for APV, with 20 from oral swab samples, 4 from cloacal swab samples, and 72 from paired oropharyngeal and cloacal swab samples. Two studies screened APV in oral swab samples, whereas cloacal swab and paired oropharyngeal and cloacal swab samples were separated in one study. One study involving 33 tissue biopsies and skin swab samples was excluded because it did not mention the virus in which sample types accordingly (Pérez-Tris et al., 2018). The pooled prevalence of APV in tissue samples was 38% (95% CI = 20–55, I^2 = 0%), and the pooled prevalence of APV in swab samples was 13% (95% CI = 5–21, I^2 = 83%), as shown in Figures 3(a) and 3(b), respectively. Only one study screened APV in fecal material, where 4 out of 968 (0.4%) samples were positive for APV.

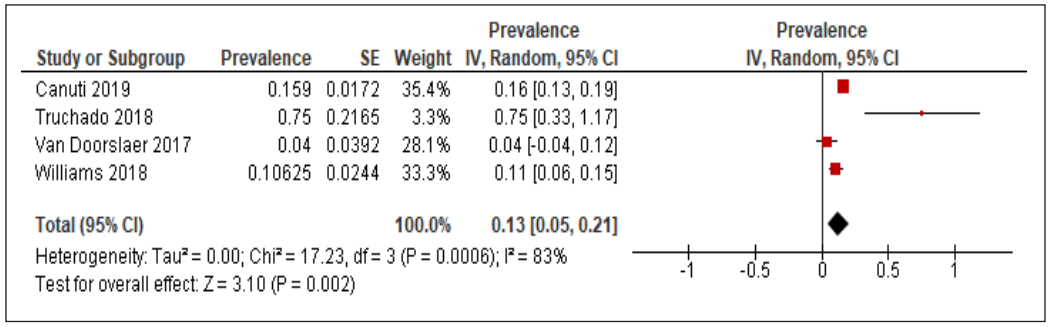
Out of the 711 samples, 68 birds were symptomatic, and 6 birds were asymptomatic, while clinical symptoms were not mentioned in the remaining 637 birds. The reported symptoms include the appearance of papillomas, pododermatitis, breathing problems, and lesions at the eyelid, leg, beak, head, and toe. Two birds with positive APV infection were reported dead. Only two studies screened for APV in both symptomatic and asymptomatic birds. The meta-analysis showed no significant occurrence of APV cases in asymptomatic birds and symptomatic birds (pooled OR = 2.89, 95% CI = 0.27–31.32, p = 0.71) (Figure 3(c)).

DISCUSSION

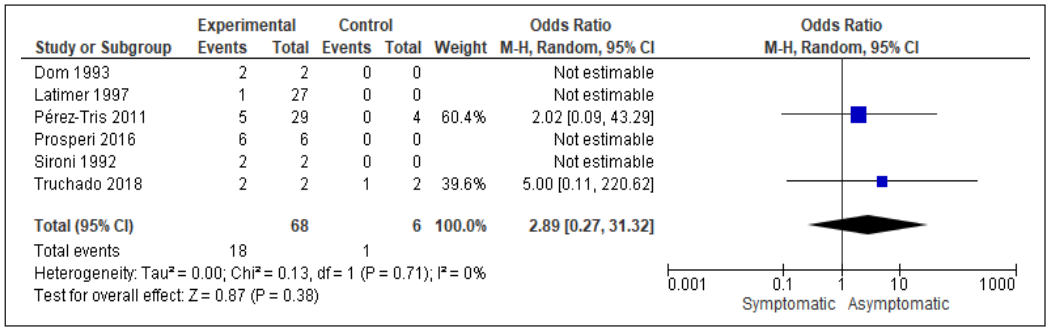
This study systematically collated published literature on the detection of APV in non-mammalian species, particularly in bird species, to observe the distribution of APV. This meta-analysis also aimed to determine the most favorable sample materials for APV screening. The information regarding accuracy parameters, such as sensitivity, specificity, true/false-positive, and true/false-negative values, was insufficiently provided in the studies included in the analysis. As such, a meta-analysis on the



(a)



(b)



(c)

Figure 3. Forest plot of random-effect meta-analysis of avian papillomavirus (AVP) screened in (a) tissue biopsy samples, (b) swab samples, and (c) symptomatic vs. asymptomatic birds. Data shows the pooled prevalence of APV in tissue samples higher than in swabs, and no significant occurrence of APV cases in symptomatic birds compared to asymptomatic birds

diagnostic accuracy of APV screening was not performed.

Based on our findings, APV is highly distributed among the families Fringillidae, followed by Laridae and Anatidae. The high prevalence of APV in the American black duck population and a lower circulation rate in mallards were related to seasonality in infections (Canuti et al., 2019). There is also an assumption that the sexual route is

a possible viral transmission mode because APV was significantly more prevalent in adult ducks during the pre-breeding season (Canuti et al., 2019; Williams et al., 2018).

Five studies performed APV screening on the wild birds, whereas four performed screening on birds at the aviary, with one of the studies screenings on both wild and aviary birds. The incidence of APV infection among wild bird populations is found to be low (Prosperi et al., 2016). Nonetheless, the species-specific nature of the virus allows local transmission even with no direct cutaneous or mucosal contact, which may jeopardize the health status of either captive or wild bird populations. The prevalence of APV from tissue and swab samples was 38 and 13%, respectively, with only one study screened from fecal material (0.4%). As such, this study did not compare the reliability between these three samples. APV commonly infects the cloaca; hence, feces are preferable to other sample materials (Varsani et al., 2015). Besides, fecal sampling is considered a fast and noninvasive screening technique since it requires no physical contact and does not cause stress to exotic birds (Zanon et al., 2018). However, a study, which conducted virus screening in only fecal or swab samples, reported a lower incidence rate (Williams et al., 2018) compared to screening in paired oropharyngeal and cloacal swabs samples (Canuti et al., 2009). There were cases of APV detection in oropharyngeal swab samples but not in cloacal swabs (Canuti et al., 2009). It affirms the importance of selecting the correct sample materials to avoid false-negative results.

A specific, sensitive, and rapid method is important to improve our knowledge of the agents causing avian cutaneous lesions. Initially, the primary investigation method for avian papillomatosis relied on histologic examination of the lesions. This method involved tissue fixation, staining, and optical microscope observation (Di Francesco et al., 2019). There was no identity confirmation of the causative agents following histologic examination. As such, the unknown causative agent can be any papilloma-caused virus or bacteria. Electron microscopy provides evidence of PV in symptomatic samples based on the virus particle. PVs can be differentiated from other viruses based on their non-enveloped icosahedral structure with a diameter of 50–60 nm (Doorbar et al., 2015). Using negative contrast electron microscopy, Sironi and Gallazi (1992) demonstrated that PVs in green finches were 52.6 nm in diameter. However, the intranuclear rounded PV-like particles in canaries were shown to be smaller, i.e., approximately 45 nm in diameter (Dom et al., 1993). The same study reported that the smaller size might be due to the fixation artifacts in the ultrathin sections compared to negative staining electron microscopy (Sironi & Gallazi, 1992). A molecular diagnostic technique, polymerase chain reaction (PCR), was developed to detect the presence of PVs in avian species. Most PCR techniques target the *L1* gene due to its highly conserved region (Padzil et al., 2021; Van Doorslaer et al., 2016).

A multiplex PCR was developed to screen more than one papilloma-causative agent, PV, and poxvirus concurrently (Pérez-Tris et al., 2011; Truchado, Williams, et al., 2018). Thus, molecular diagnostic provides reliable results as they can differentiate the absence or presence of the target organisms.

APV infection is usually characterized by papilloma lesions at the base of the tongue or on the glottis among psittacines (Truchado, Williams et al., 2018). The infection of certain APVs, such as FcPV1, FgPV1, and PePV1, is associated with cutaneous papillomas (Jones et al., 2020). However, the occurrence of APV infection is not always presented in the clinical symptoms of the disease. The meta-analysis showed no significant APV cases in asymptomatic and symptomatic birds. Besides, there are cases where PV is not detected in birds, despite showing clinical signs (Di Francesco et al., 2018; Johne et al., 2002; Jones et al., 2020). It is due to the other viruses or bacteria that can cause similar clinical signs with PV infections. For example, viruses like poxvirus and herpesvirus may cause the development of nodules or papillomas, while bacterial abscesses or neoplastic diseases may cause epithelial tumors and soft tissue sarcomas (Di Francesco et al., 2018; Johne et al., 2002; Pérez-Tris et al., 2011). To further validate and reduce the gap of knowledge of APV occurrences in asymptomatic birds and symptomatic birds, increasing the number of APV screenings is recommended.

This study encountered several limitations, i.e., (1) the sample number varied from as low as 2 to 452 bird samples, thus did not provide a standardized data comparison, (2) few studies did not specifically mention the pre-deposited clinical signs of birds, either they were symptomatic or asymptomatic, (3) the diagnostic techniques were varied among those included studies, which might cause an argument in the meta-analysis study, and (4) a high heterogeneity in the results was also observed despite the small number of reviews being included. It was believed to be due to the random effects model, which was selected as the meta-analysis model. A further subgroup analysis or meta-regression model, which includes study settings, sample size, publication year, and phenotype search terms (Sun & Feng, 2019), can be explored in future work. Additionally, a reliability comparison can be conducted by reproducing the experiments to confirm the findings.

CONCLUSION

APV is most prevalent among three families, i.e., the Fringillidae, Laridae, and Anatidae. The distribution of APV among wild and captive birds could not be predicted efficiently due to insufficient rapid diagnostic kits targeting APV of birds compared to other species such as bovines and humans. Using paired samples in the virus screening is important because inconsistent results can occur in different sample materials collected from the same bird. However, the prevalence of APV in tissue samples is high, which can be used as a single sample material. The occurrence of APV cases among

symptomatic and asymptomatic birds is not significant. It was assumed that a high virus load is needed to develop the clinical signs among infected birds. Thus, this meta-analysis study helps determine the most suitable sampling methods for retrieving the PV in avian species. The information gathered from this study can significantly increase the chances of isolating the APV from tissue samples and studying them on molecular and structural levels.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

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